DESIGN AND *IN VITRO* EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF METOPROLOL TARTRATE

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Submitted by

Miss BINCY MARY KOSHY

Under the guidance of

Prof. S. KUPPUSAMY, M.Pharm.,

Department of Pharmaceutics

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Coimbatore – 641044

Certificate

This is to certify that the dissertation entitled ***"DESIGN AND INVITRO EVALUATION OF TRANSDERMAL DRUG DELIVERY SYSTEM OF METOPROLOL TARTRATE"*** *was carried out by* **Miss. BINCY MARY KOSHY**, *in the Department of Pharmaceutics, College of Pharmacy, Sri Ramakrishna Institute of Paramedical Sciences, Coimbatore, which is affiliated to the Tamilnadu Dr. M.G.R. Medical University, Chennai, under my direct supervision and complete satisfaction.*

Prof. M. Gopal Rao, M.Pharm., (Ph.D.)
Head - Department of Pharmaceutics,
College of Pharmacy,
SRIPMS,
Coimbatore - 641
044.

Place: Coimbatore
Date:

Certificate

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Prof. S. KUPPUSAMY, M.Pharm.,
Department of Pharmaceutics,
College of Pharmacy,
SRIPMS,
Coimbatore –44.

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Dr. T. K RAVI, M. Pharm., Ph.D., FAGE
Principal,
College of Pharmacy,
SRIPMS,
Coimbatore-641 044.

Place: Coimbatore

Date:

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LIST OF ABBREVIATIONS

MT	-	Metoprolol Tartrate
PVP	-	Poly vinyl pyrrolidone
CAB	-	Cellulose acetate butyrate
EC	-	Ethyl cellulose
HPMC	-	Hydroxy propyl methyl cellulose
IPM	-	Isopropyl myristate
TDDS	-	Transdermal Drug Delivery System
DBP	-	Di butyl phtalate
FDA	-	Food and Drug administration
IR	-	Infra red
PSA	-	Pressure Sensitive Adhesive
PIB	-	Poly Isobutylene
UV	-	Ultraviolet
IP	-	Indian pharmacopoeia
OTC	-	Over the Counter
BP	-	British pharmacopoeia
USP	-	United States Pharmacopoeia

INTRODUCTION

This century has witnessed several spectacular developments in the field of pharmaceutical sciences especially in the drug delivery systems. [1]Throughout the past two decades, the transdermal patch has become a proven technology that offers a variety of significant clinical benefits over other dosage forms.

[2]Transdermal drug delivery systems have been developed, aiming to achieve the objective of systemic medication through topical application to the intact skin. Because transdermal drug delivery offers controlled release of drug into the patient, it enables a steady blood level profile, resulting in reduced systemic side effects and sometimes, improved efficacy over other dosage forms. In addition transdermal patches are user friendly, convenient, painless and offer multiday dosing, it is generally accepted that they offer improved patient compliance.

"Transdermal drug delivery is defined as self contained, discrete dosage form which when applied to the intact skin, deliver the drug through the skin at controlled rate to the systemic circulation".

Transdermal drug delivery system is a means by which a pharmacologically active moiety may be continuously delivered systemically in an efficient, reliable and safe manner. They are capable of better performance than conventional delivery by monitoring the concentration, location and duration of drug action.

Transdermal product has been in a significant upward trend and that is likely to continue for the foreseeable future. [3]The first adhesive transdermal delivery system (TDDS) patch was approved by the Food and Drug Administration in 1979 (scopolamine patch for motion sickness). Nitroglycerine patches were approved in 1981. [4]Transdermal clonidine was approved by the US Food and Drug Administration 1984 for the treatment mild-to-moderate hypertension alone or in combination with diuretic. This method of delivery became widely recognized when nicotine patches for smoking cessation were introduced in 1991.

Over the past two decades, more than 35 transdermal products have been approved generating sales of $3.2billion in 2002, which is predicted to rise to $4.5billion in 2008. This rapid increase in the market value has lead to transdermal drug delivery becoming one of the fastest sectors within pharmaceutical industry.

Conceptual Origin of TDDS[5]

The potential of using intact skin as the part of drug administration has been recognized for several decades, as evidenced by development of medicated plasters. Transdermal delivery of medications was foreshadowed in earlier era by the use of certain plasters and ointments.

Historically medicated plaster can be viewed as the first development of transdermal drug delivery. It is designed to bring medication into close contact with skin so that drug can be delivered transdermally.

The use of medicated plasters could be traced several 100 years back in ancient China. The medicated plaster has also been very popular in Japan and many are available as OTC pharmaceutical dosage forms, commonly called cataplasms. In United States the following three medicated plasters have been listed in official compendia namely belladonna plaster, mustard plaster and salicylic acid plaster. These plasters are rather simple in formulation and were developed mainly for local medication.

Developments in Transdermal Drug Delivery

The skin was thought to be an impervious barrier. At the turn of the century, during World War II, munitions workers experienced less angina attacks while working with Nitroglycerin. This has challenged the traditional belief that the skin is a perfect barrier and also triggered intensive research activities to study the feasibility of transdermal drug delivery for systemic medications. Several Transdermal Drug Delivery Systems (TDDS) have been developed recently, with the aim of accomplishing the objective of systemic medication through the transdermally controlled delivery of pharmaceuticals. The potential of TDDS was first demonstrated by the successful development of scopolamine releasing TDDS (Transdermal scop system/ Ciba) for 72 hrs prophylaxis or treatment of motion sickness and nausea then by marketing success of this TDDS. Several products were introduced immediately, some of them are Nitroglycerin- releasing TDDS for once-a-day medication of angina pectoris, clonidine- releasing TDDS for weekly therapy of hypertension and Estradiol- releasing TDDS for twice -a- week treatment for menopausal syndrome.

In addition to the currently marketed formulations, new drugs are being formulated using transdermal systems because of the inherent advantage of administration by this route. Buslpar, an anti-anxiety agent and the combination of Mecamylamine, for smoking cessation therapy are being developed for TDDS and are currently undergoing phase-III clinical trials.

Even it has been said that TDDS can be given to newborn infants, IV therapy to infants is difficult and painful. Absorption of the drugs by oral therapy may be erratic to infants. The skin of preterm infants is more permeable to drugs. As dose requirements are very small in infants, the permeability is high and TDDS may be more useful. However lot of precautions and care must be taken during the administration of TDDS to infants and it is also said that transdermal formulations containing antibiotic combination gives better treatment for second-degree wounds.

Potential Benefits of TDDS[6]

- Steady state infusion of drug over an extended period of time.
- TDDS can decrease the therapeutic failure of many drugs and avoids problem associated with the drug like first pass effect, decomposition of drugs and GI irritations.
- Improved patient compliance due to simplified medication regimen.
- It permits continuous drug administration and the use of drug with short biological half-life.
- Multi day therapy with single application.

- Self medication is possible.
- Minimise inter and intra patient variation.
- It avoids the risks and inconvenience of IV therapy.
- Termination of medication is possible at any time if needed by simply removing the TDDS from skin surface.
- Provides predictable extended duration of activity.

Limitations of TDDS[7]

- TDDS cannot be used for all drugs.
- The drug must have desirable physical chemical properties for penetration through stratum corneum.
- Skin irritation or contact dermatitis.
- Only low dose drug can be used.
- Variable intra and inter individual percutaneous absorption efficiency.
- High cost.

Skin Structure and Barrier Properties[5]

Human skin is uniquely engineered organ that permits terrestrial life by regulating heat and water loss from the body whilst preventing the entry of noxious chemicals or micro organisms. It is the largest organ of the human body providing around 10% of the body mass of an average person and it covers an average area of $1.7m^2$. Whilst such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions. Human skin is a highly efficient self repairing barrier designed to keep “inside in and outside out”.

For the purpose of TDD the structure and function of human skin is categorized into four main layers.

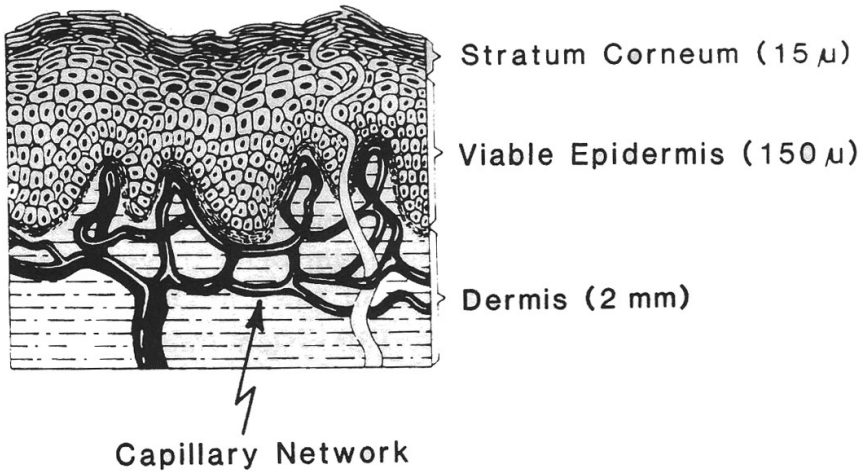


Fig 1

The structural relationship among stratum corneum, viable epidermis, and the capillary network at the dermoepidermal junction

1. The outer most layer of tissue (a nonviable epidermal layer), the stratum corneum.
2. The viable epidermis.
3. The overlying dermis.
4. The innermost subcutaneous fatty layer, hypodermis

The Stratum Corneum

It is horny layer which is rate limiting barrier that controls the inward and outward movement of chemical substances.

The stratum corneum typically comprises 10-15 cell layers. This membrane consisting of dead, nucleate cells embedded in lipid matrix is essential for controlling the percutaneous absorption of most

drugs and chemicals. The barrier nature of the horny layer depends critically on its constituents, 75 - 80 % proteins, 5-15% lipids and 5-10% unidentified materials on a dry weight basis. The protein fraction predominantly comprises of keratin filaments which are cross linked by inter molecular disulfide bridges.

The Viable Epidermis

The epidermis is a layer which comprises of the rapidly dividing basal cells. Migration of active epithelial basal cells towards the skin surface forms, thin stratified and extremely resilient layer at the skin surface called stratum corneum. Below this layer are the other layers of epidermis that is stratum lucidum, stratum granulose, stratum spinosum and stratum basale or germinativum.

The Dermis

The dermis is 3-5mm thick and is composed of a matrix of connective tissue in which predominant bundles of collagen fibrils interlace with elastic tissue and sparse reticular fibers. The dermis encloses cutaneous appendages and is penetrated by blood vessels, lymphatic and nerves

In terms of TDDS this layer is viewed as essentially gelled water and thus provides a minimal barrier to the delivery of most polar drugs, although dermal barrier may be significant when delivering highly lipophilic molecules.

The Innermost Subcutaneous Fatty Layer

The fatty layer bridges between the overlying dermis and the underlying body constituents. This layer of adipose tissue principally serves to insulate the body and to provide mechanical protection. It can also provide a readily available supply of high energy molecules while the principal blood vessel nerves are carried to skin in this layer.

FUNDAMENTALS OF SKIN PERMEATION

Transdermal permeation is depended on three steps:

- Sorption of stratum corneum
- Penetration of drug through viable epidermis.
- Uptake of drug by the capillary network in the dermis.

The rate of permeation, dQ/dt across the skin tissues can be expressed mathematically by the following relationship

$$\frac{dQ}{dt} = P_s(C_d - C_r)$$

Where C_d and C_r, respectively are the concentration of skin penetrant in the donor compartment e.g. the concentration of drug on the stratum corneum surface as delivered from a TDD system, and in the receptor phase, e.g. systemic circulation; and Ps is the overall permeability coefficient of the skin tissues to the penetrant and is defined by

$$Ps = \frac{K_{s/d}\, D_{ss}}{h_s}$$

Where $K_{s/d}$ is the partition coefficient, for the interfacial partitioning of a penetrant molecule, from the solution medium or a transdermal therapeutic system on to a stratum corneum;Dss is the apparent

diffusivity for the steady state diffusion of the penetrant molecule through the skin tissues for penetration ; and h_s is the overall thickness of the skin tissues for penetration.

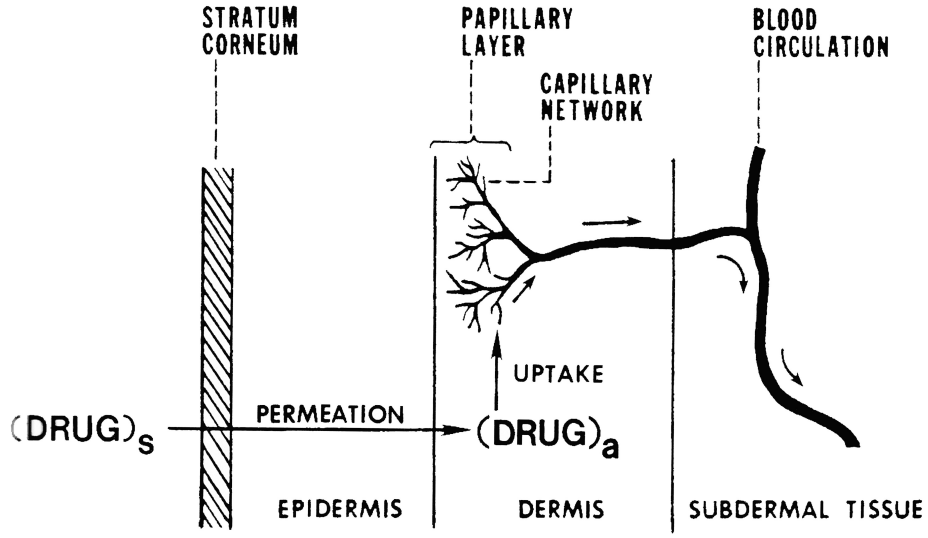


Fig 2

Multilayer skin model showing the sequence of transdermal permeation of drug

This suggests that to achieve a constant rate of drug permeation one needs to maintain the drug concentration on the surface of the stratum corneum (C_d) consistent and substantially greater than the drug concentration in the body (C_r) i.e.$C_d > C_r$

Under such conditions equation is reduced to

$$\frac{dQ}{dt} = P_s C_d$$

The rate of skin permeation d_Q/d_t becomes a constant if the magnitude of C_d remains fairly constant throughout the course skin permeation. To maintain C_d at a constant value it is necessary to make

drug release at a rate (Rd) that is either constant or always greater than the rate of skin uptake (Ra) i.e. $R_d > R_a$

By making Rd greater than Ra, the drug concentration of the skin surface, (C_d) is maintained at a level equal to or greater than the equilibrium (or saturation). Solubility of the drug in the stratum corneum (C^e_s) i.e. $C_d > C^e_s$ and a maximum rate of skin permeation dq/dt is expressed as

$$\left(\frac{dQ}{dt}\right)_m = P_s C^{e}{}_s$$

The maximum skin permeation rate depends upon the permeability coefficient and equilibrium solubility of drug in stratum corneum. Thus permeation appears to be stratum corneum limited.

FACTORS AFFECTING BIOAVAILABILITY OF TDDS

It consists of physiological and formulation factors

PHYSIOLOGICAL FACTORS

Stratum corneum

Transdermal bioavailability depends upon the barrier function of the stratum corneum. For very lipophilic compounds, it is generally believed that transport is limited not by diffusion across the stratum corneum, but rather by kinetics with which the molecule leaves the membrane and enters the underlying viable epidermis.

Anatomic site

The extent of absorption depends upon the anatomical sites to which the compound is applied. Likewise in TDDS, certain regions are significantly more permeable.

Skin condition and disease

Stages in barrier function due to skin diseases generally result either from alteration of the lipid/protein composition of the stratum corneum

Age

Like anatomic site, skin age is also believed to impact upon percutaneous absorption and transdermal bioavailability.

Skin metabolism

Presystemic metabolism in the skin can obviously modify transdermal drug bioavailability.

Skin irritation and sensitization

These responses are provoked by such diverse stimuli such as UV radiation, soaps, poisons, and of course, tropically applied drugs and other components of transdermal formulations.

FORMULATION FACTORS

Physicochemical property of transport

Permeation through the stratum corneum occurs by passive diffusion, a process well defined by ficks first law and second law. The rule of the formulation and that of the physicochemical properties of the drug on transdermal bioavailability can now be readily appreciated because at steady state, there is direct relationship between J and plasma concentration (Css) achievable.

Rate in A*J= Rate out Cl*Css

Where Cl is the drug clearance and it follows J, the instantaneous flux, which depends upon two parameters properties of the formulation and

of the drug (i.e. Kp and Cr) directly determines that the drug target plasma concentration is attainable or not when the area of contact between the delivery system and the skin (A) is reasonable.

BASIC COMPONENTS OF TDDS[8]

The various materials used in TDDS are on the basis of functional classification of the various components. The basic components of transdermal devices are polymeric matrices or reservoirs, drug, permeation enhancers and other excipients.

Polymers for Transdermal Delivery

[9]Polymers are the backbone of the transdermal drug delivery system. The polymer controls the release of drug from the devices. The following criteria should be satisfied for a polymer to be used in transdermal system.

- Drug solubility and diffusivity in the polymer.
- The desired drug loading and its effect on polymer integrity.
- Compatibility of the polymer with necessary excipients, such as solvents and skin permeation enhances for the drug.
- Skin compatibility: the effect of moisture occluded under the polymer formulation.
- Mechanical properties: softness, flexibility, conformability to skin and mechanical integrity.
- Ease of fabrication.
- Toxicity and purity.
- Cost and availability.

It is rare to find a commercial polymer that satisfies all the above criteria for polymer selection. Hence various techniques have been employed to modify the polymer properties and thus drug release rates.

Cross linked polymers: The higher the degree of cross linking the more dense the polymer and slower the diffusion of drug molecule through the matrix. Cross-linking may be achieved chemically using cross –linking agent or by irradiation.

Polymer blends: The blended polymer combines the advantages of individual polymers. The potential advantages include easy fabrication of devices, manipulation of drug loading and other device properties such as hydration, degradation and mechanical strength.

Plasticizers: Plasticizers are used to reduce the stiffness of the polymer backbone thereby increasing the diffusion characteristics of the drug. In selection of plastizers care must be taken to select a material which is biocompatible.

COMMONLY USED POLYMERS IN TDDS[10]

Polyisobutylene

Polyisobutylene is a highly paraffinic, non-polar and amorphous hydrocarbon polymer composed of essentially straight chain macromolecules. Physical properties of PIB change gradually with increasing molecular weight, the liquids are become more viscous, then change to balsam like sticky masses, and finally form elastomeric solids. PIB is soluble in hydrocarbon solvents and

insoluble in polar solvents. PIB exhibits excellent low- transition temperature flexibility and oxidative stability.

Polyacrylates

Copolymers of acrylic and methacrylic acid ester can be most suitable for use as drug/ polymer matrix. Acrylate polymers, which are moderately polar, colorless and transparent, have excellent chemical resistance, thermal, light and oxidative stability.

Poly siloxanes

Polysiloxanes also referred to, as silicones are organo silicon polymers having si-o-si bonds along main chain and an alkyl group attached to a significant proportion of silicon atoms by silicon carbon bonds. These silicones have high thermal and oxidative stability, chemical inertness and very low surface tension.

Hydrogels

Hydrogels are water swollen but water insoluble cross-linked networks of hydrophilic polymers. They can absorb water by more than 20% of its dry weight. The drug/hydrogel matrix can be prepared by either incorporating the drug in aqueous polymerization mixture or by equilibrium of the hydrogel in concentrated aqueous solution of the drug.

Polyvinyl Pyrrolidones

It is white, odourless and hygroscopic powder. It is available in different viscosity grades, identified by K values. It acts as antinucleating agents that retard the crystallization of a drug. Thus they play a significant role in improving the solubility of a drug in the

matrix by sustaining the drug in an amorphous form so that it undergoes rapid solubilisation by penetration of the dissolution medium.

Poly Vinyl Alcohol

It is cream coloured granular powder and is prepared from polyvinyl acetates. PVA is available in different grades and the viscosity is directly proportional to its molecular weight.

Ethyl vinyl acetate (EVA) polymers

EVA frequently used to prepare rate controlling membranes in transdermal delivery systems because it allows the membrane permeability to be altered by adjusting the vinyl acetate content of the polymer. They have been shown to be chemically stable, non-toxic and biocompatible.

Cellulose derivatives

Many cellulose derivatives are employed for transdermal drug delivery like ethyl cellulose, methyl cellulose, cellulose acetate phthalate, cellulose acetate butyrate, hydroxyl propyl methyl cellulose, sodium carboxy methyl cellulose. They are commonly used in combination with hydrophilic polymers like PVP, PEG etc.

SELECTION OF DRUG CANDIDATES FOR TDDS

The choice of drugs to be delivered is almost a difficult one and careful consideration should be given for selection of suitable drug molecules. It depends on the physicochemical and biological properties of the drug.

Physicochemical properties of the drug

- The drug should have a molecular weight less than 750.
- It should have affinity for both lipophilic and hydrophilic phase.
- It should have low melting point.

Biological properties of the drug

- The drug should be potent with a daily dose of few mg/day.
- It should have short half life
- The drug should not stimulate an immune reaction in the skin.
- The drug must not induce a cutaneous irritant or allergic response.
- The drug having high first pass metabolism is suitable candidate for TDDS.

PENETRATION ENHANCERS

The success of transdermal drug delivery depends on the ability of the drug to permeate skin in sufficient quantities to achieve required therapeutic plasma levels. Unfortunately many drugs do not possess intrinsically, any ability to cross the skin, and ways must be found to modify the barrier. This can be achieved by the use of permeation enhancers or physically by iontophoresis and sonophoresis.

Chemical penetration enhancers

The penetration enhancers are agents that increase the permeability of the skin or substances that temporarily reduce the impermeability of the skin.

The properties of an ideal penetration enhancer are

- Pharmacologically inert
- Odourless, tasteless, colorless
- Non-toxic, non-irritating, nonsensiting and non allergic
- Rapid onset of action, predictable and suitable duration of action for drug used
- Rapidly incorporated into the delivery system.
- Following removal of enhancer, the stratum corneum should immediately and fully recover its normal barrier property
- Chemically and physically compatible with the delivery system
- Inexpensive and cosmetically acceptable

Commonly Used Chemical Enhancers

1. Sulfoxides and similar compounds

Ex: dimethyl sulfoxide (DMSO), isopropyl myristate(IPM)

2. Pyrrolidones

Polyvinyl pyrrolidone

3. Azones

4. Surfactant

Anionic laurate ions have the greatest penetration and strongest permeation promotion action.

OTHER EXCIPIENTS

Adhesives

The adhesives should be having following properties

1. Excellent contact with the skin.
2. Non-irritant, physically and chemically inert to the drug.

3. Should be easily removed.
4. Should not affect permeation process.
5. Should be non-irritant, non-sensitizing

Pressure sensitive adhesives (PSA) have found application in transdermal drug delivery because of the need to intimate contact between the transdermal system and skin surface. The adhesive bond formation involves a liquid like flow process resulting in adhesive wetting of the skin surface upon application of pressure. When the pressure is removed, the adhesive sets in that state. The PSA is a characteristic of a visco elastic material, significantly above its glass-transition temperature.

Commonly employed PSA in TDDS include acrylate copolymers, polyisobutylene and polysiloxanes. Acrylic –based adhesives are less irritating than silicone adhesives and the migration of ingredients into the adhesive during storage may also be less compared to other types.

Backing Layer

The backing layer must be impermeable to the drugs and other components of the device and also it should be impermeable to water vapour i.e. occlusive. The most commonly used backing materials are polyester and polyethylene films. The films can be either clear (Estraderm) flesh coloured (Catapres-TTS) or metallized (Transderm scop) . Other non-porous plastics with similar properties could equally well be used. If the entire area, under the patch is active and the patch is not extensively large, then it is probably most convenient to use an

occlusive backing. If the patch has a central area, containing the drug surrounded by a ring adhesive and the size of the patch is relatively large, the wearers comfort may be increased by having a backing material that is non occlusive.

Peel Strip

The peel strip prevents drug loss when it has irrigated into the adhesive layer on storing and protects the finished device against contamination. The requirements for the peel strip are essentially the same as those for occlusive backing. The impermeable easily peelable films are made of polyester, foils etc.

TECHNOLOGIES OF TRANSDERMAL DRUG DELIVERY SYSTEMS[6]

Several technologies have been successfully developed to provide mechanism of rate control over the release and transdermal permeation of drugs. To be precise, there are two concepts in the design of TDDS namely skin controlled device (matrix type) and system controlled device (reservoir type). The others are extensions of these two concepts.

Matrix System

It is designed to rely on the skin to control the rate at which drug diffuses into the body. Skin controlled devices are typically monolith systems that incorporate a drug in matrix layer between frontal and backing layer. The polymer matrix controls the release rate (proportional to the square root of time) which is generally greater than permeation rate across the skin.

Membrane System

The transdermal system provides majority of the control of the rate of drug input to the body. System controlling devices contain a rate controlling membrane and drug (usually in liquid or general form) in a reservoir, backing, adhesive and protective layer. This type of system is beneficial when the desired rate of drug transport is considerably less than that through the skin.

Polymer Membrane Permeation - Controlled System

In this system, the drug reservoir is encapsulated in a compartment molded from a drug impermeable backing layer and a rate controlling polymeric membrane.

In the drug reservoir compartment, the drug particles are either dispersed in a solid polymer matrix or suspended in an unleachable, viscous liquid medium. On the external surface, a thin layer of drug compatible adhesive polymer. e.g.: silicone or polyacrylate adhesive is applied to provide an intimate contact between device and skin surface.

Matrix Diffusion Controlled Systems

The drug reservoir in this type of device is formed by homogenously dispersing the drug particles in a hydrophilic or lipophilic polymer and the medicated polymer is then molded into a medicated disc and then glued to a base plate, which is sealed to a drug impermeable backing. Most of these systems do not have adhesive over layers but instead possess a peripheral adhesive ring.

Adhesive Diffusion Controlled Systems

In this the drug reservoir is formulated by directly dispersing the drug in an adhesive polymer on a flat sheet of drug impermeable backing to form a thin drug reservoir layer. Layers of non medicated rate controlling adhesive polymer of constant thickness are applied to produce an adhesive diffusion controlled drug delivery system.

Microreservoir or Microsealed Controlled System

These systems are a combination of the reservoir and matrix dispersion type drug delivery systems. In these systems, drug dispersions is prepared by suspending the drug in an aqueous polymer solution and then the drug suspension is dispersed homogenously into lipophilic polymer by high shear mechanical force, to form microscopic spherical reservoir with the drug entrapped. Cross linking the polymer chains by the addition of polymeric cross linking agents stabilizes this unstable dispersions. This matrix is then attached to an adhesive foam (flexible) backing. The system has a peripheral adhesive ring

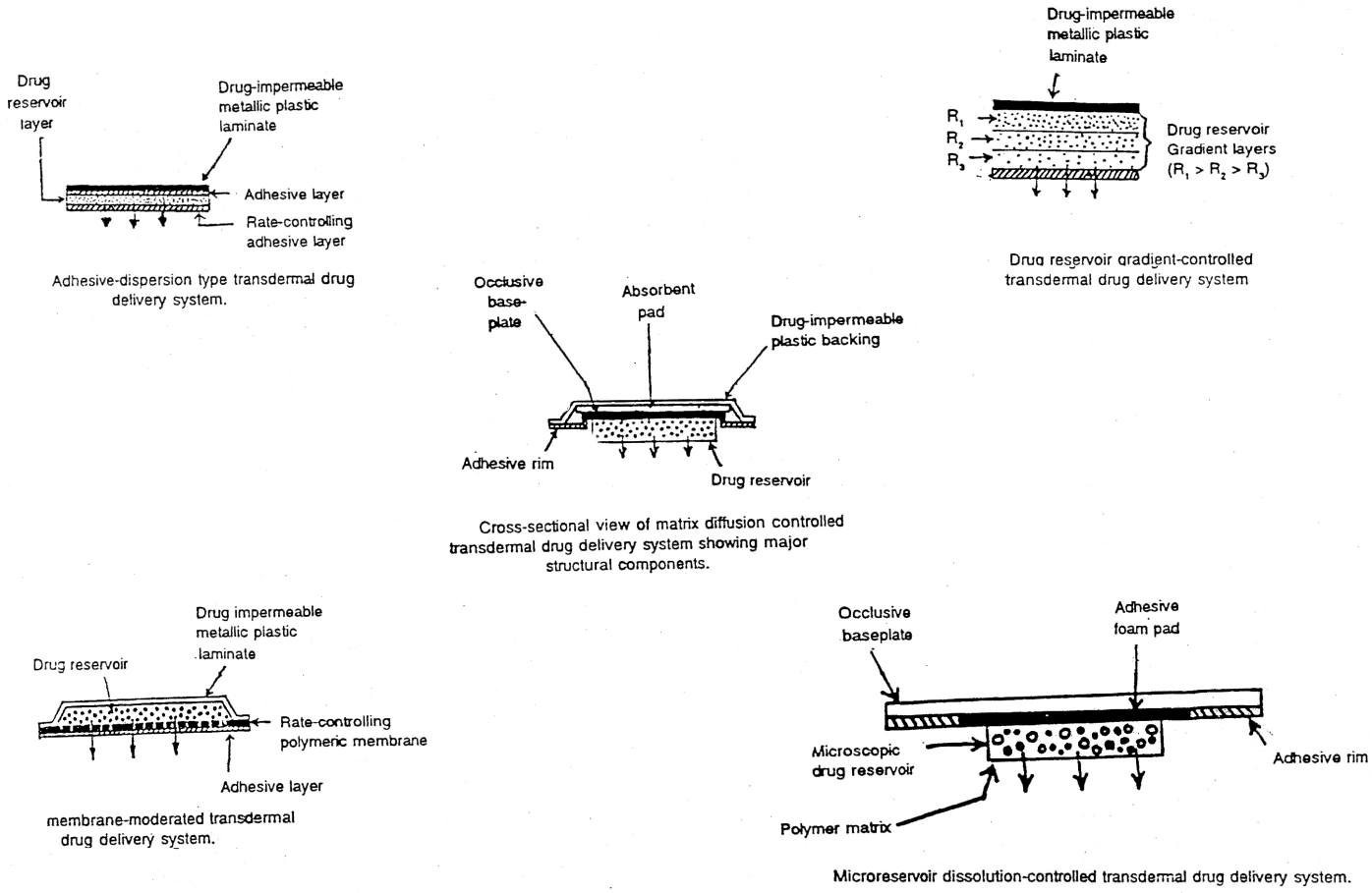


FIG 3
Different types of transdermal drug delivery systems

VARIOUS APPROACHES TO INCREASE DRUG PENETRATION[11]

Drug absorption across the skin is very low due to the stratum corneum (the main barrier for drug absorption across the skin). Overcoming the penetration barrier would significantly improve the development of an efficient transdermal drug delivery system. Several techniques have been developed, or are under development, to bypass the stratum corneum. The most common approach has been the inclusion of chemical permeation enhancers (e.g.:isopropyl myristate) in topical formulation. These substances increase the drug penetration by altering skin barrier functions; in particularly, this absorption promotes target the outermost layer of epidermis, the stratum corneum.

However, from a pharmaceutical stand point although chemical enhancers are appealing because they may be readily incorporated into a formulation, they suffer from a number of drawbacks because to achieve their goal (i.e. to perturb the skin barrier). Such substances are either irritating or induce an inflammatory reaction in response to the application to the barrier. Furthermore, their nonselectivity means once the skin barrier is compromised, the entry of substance other than active drug is also facilitated. Other methods used for getting drugs into the blood stream quickly and efficiently through the skin include iontophoresis, ultrasound, radiofrequencies and micro needles.

Iontophoresis

It applies a small voltage (typically 10 V or less) continuous constant current (typically 0.5m A/ cm^2) to push a charged drug into skin or other tissue. Iontophoresis can enhance delivery by driving charged compounds across the skin by a direct interaction with the electric field. Those with the greatest charge, and smaller molecules, get across quickest. The potential of this technique is recently being rediscovered for transdermal systemic delivery of ionic drugs including peptides and oligonucleotides, which are normally difficult to administer, by parenteral route. The technique has been observed to enhance transdermal permeation of ionic drugs several fold, and this can expand the horizon of transdermal controlled drug delivery for systemic medication. Besides the typical advantages of transdermal delivery, iontophoresis presents a unique opportunity to provide programmable drug delivery.

This is because the drug is delivered in proportion to the current, which can be readily adjusted. Such dependence on current may also make drug absorption via iontophoresis less dependent on biological variables. Also patient compliance can be improved by including electronic means to remind patients to replace the dose when required.

Electroporation

It involves application of high voltage pulse for a very short duration to permeabilise the skin. The change in the membrane involves structural arrangement and conductance leading to temporary loss of pores. Approximately 100 multilamellar bilayers of the stratum corneum need about 100v pulses for electroporation or 1v per bilayer.

Sonophoresis

Ultrasound has been used to treat a wide range of clinical conditions and to transport drugs to deeper tissues in the treatment of inflammatory conditions. The technique involves placing and massaging the area with an ultrasonic source. Recently sonophoresis has attracted lot of interest in transdermal delivery with the focus on peptide protein delivery.

Microfabricated Microneedles and Microchips Technology

Recently, a novel method was developed for enhancing transport of molecules across the skin. The micro fabricated micro needles technology employs micron- sized needles made of silicon.

These micro needle arrays after insertion into the skin create conducts for transport of drug across the stratum corneum. The drug after crossing the stratum corneum diffuses through the deeper layers and taken up by the capillaries for systemic administration. Micro needles penetrate the skin about 10-12 µm deep inside the skin but do not reach the nerves found in deeper tissue, so are painless. The micro needles were made using the micro fabrication technology similar as making of integrating circuits. A microprocessor is attached to a tiny

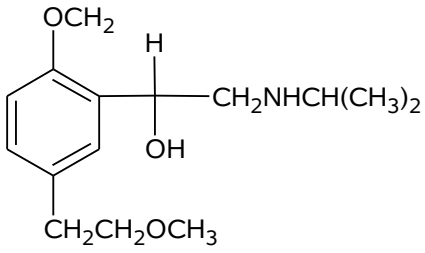
pump for delivering tiny amounts of the drug. The microprocessor and pump automatically injects the right dosage of drug. Micro needles have extremely sharp tips with a radius of curvature less then 1 mm facilitating easy piercing into the skin. The micro fabrication technique can be easily modified to make longer or shorter needles according to the requirements.

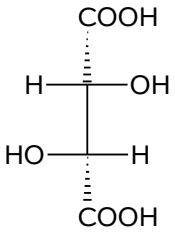
Laser Radiation

This method involves direct and controlled exposure of a laser to the skin which results in the ablation of stratum corneum without significantly damaging the underlying epidermis. Removal of stratum corneum by this method has been shown to enhance the delivery of hydrophilic and lipophilic drugs.

DRUG PROFILE

METOPROLOL TARTRATE[12]





Category : Cardioselective, antihypertensive

Molecular Formula : $(C_{15}H_{25}NO_3)_2.C_4H_6O_6$

Molecular Weight : 684.82

IUPAC Name : 1-isopropylamino -3-p - (2- methoxyethyl) phenoxy - propan -2-ol (2R, 3R) tartrate.

Dose : 100-450 mg daily, in divided doses.

M.P : 121°-124°

PHARMACOKINETICS[13]

Absorption : Orally administered metoprolol tartarte is absorbed rapidly and almost completely absorbed from the G.I. tract; food enhances the absorption.

Distribution : Distributed widely throughout the body; about 12% is plasma- bound.

Metabolism : Metabolized in the liver.

Excretion : About 95% of a given dose of metoprolol is excreted in urine within 72 hours, largely as metabolites.

PHARMACODYNAMICS

Metoprolol is classified as cardioselective $beta_1$ agonist; drug may reduce blood pressure by blocking adrenergic receptor, thus decreasing cardiac output, by decreasing sympathetic outflow from CNS or by suppressing renin release.

Description : White crystalline powder or colourless crystals.

Solubility : Very soluble in water, freely soluble in ethanol (95%), chloroform and in dichloromethane, slightly soluble in acetone, practically insoluble in ether.

Bioavailabilty[14,15] : 38± 14%

Urinary Excretion : 10±3%

Volume of Distribution : 4.2±0.7

Half Life : 3.2±0.2 hrs.

Storage : Store in tight, light resistant container at 15-30°c and metoprolol tartrate injection should be stored at a temperature of 30°c or less, preferably 15-30°c, freezing of injection should be avoided.

Standards : Metoprolol tartrate contains not less than 99% and not more than 101% of $(C_{15}H_{25}NO_3)_2C_4H_6O_6$. Calculated with reference to the dried substance.

pH : Between 2&7, determined in a 2% w/v solution.

POLYMER PROFILE

[16]POLY VINYL PYRROLIDONE

Non proprietary names:

BP : Povidone

JP : Povidone

Ph Eur : Povidonum

USPz : Povidone

Synonyms : E1201; Kollidon: plasdone; PVP: Poly [1- (2-oxo-1-pyrrolidinyl) ethylene]; polyvidone; 1-vinyl-2- pyrrolidionone polymer

3. Chemical name and CAS Registry number : 1-Ethenyl-2-pyrrolidinone homo polymer [9003-39-8]

4. Empirical formula : $(C_6H_9No)_n$

5. Molecular weight : 2500-3,000,000

Table 1: Approximate molecular weights for different grades of Povidone

K value	Approximate molecular wt
12	2500
15	8000
17	10,000
25	30,000
30	50,000
60	400,000
90	1,000000
120	3000000

6. Functional category

Disintegrant, dissolution aid, suspending agent, tablet binder

7. Description

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Povidones with K-values equal to or lower than 30 are manufactured by spray-drying and occur as spheres.

8. Typical properties

Acidity/alkalinity **:** pH = 3.0-7.0 (5% w/v aqueous solution)

True density **:** 1.180g / cm^3

Melting point **:** Softens at 150^oC

Moisture content

Povidone is very hygroscopic significant amounts of moisture being absorbed at low relative humidities.

9. Solubility

Freely soluble in acids, chloroform, ethanol, ketones, methanol and water, practically insoluble in ether, hydrocarbons and mineral oil.

10. Stability and storage conditions

Povidone darkens to some extent on heating at 150^{o}C, with a reduction in aqueous solubility. It is stable to a short cycle of heat exposure around 110-130^{o}C. Steam sterilization of aqueous solution does not alter its properties

11. Safety

Povidone has been used in pharmaceutical formulations for many years, being first used in the 1940s as a plasma expander, although it has now been superseded for this purpose by dextran.

12. Application in pharmaceutical formulation or technology

- It is primarily used in solid-dosage forms
- In tableting, povidone solution are used as binders in wet granulation processes
- It is also added to powder blends in the dry from and granulated inside by the addition of water, alcohol or hydro alcoholic solutions.
- It is used as a solubilizer in oral and parenteral formulations and has been shown to enhance dissolution of poorly soluble drugs from solid dosage forms

- Used as a suspending, stabilizing or viscosity-increasing agent in a number of topical and oral suspensions and solutions.
- The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

Special grades of pyrogen-free povidone are available and have been used in parenteral formulations

CELLULOSE ACETATE BUTYRATE[17,18]

Ph Eur	: Cellulosi Acetas Butyras
Synonym	: Cabufocon
Molecular weight	: 16000
Functional category	: coating agent, extended release agent.
Description	: a white, yellowish white or greyish white powder or granules, slightly hygroscopic.

TYPICAL PROPERTIES

Melting point	: 127-147^{0}c
Specific gravity	: 1.16
Solubility	: insoluble in water and alcohol, soluble in acetone, formic acid , chloroform and in a mixture of equal volume of methanol and methylene chloride
Stability and storage	: cellulose acetate butyrate is stable if stored in a well closed container in a cool, dry place. It hydrolysis slowly under prolonged adverse conditions such as high temperature and humidity.

Compatability : compatabile with plasticizers dibutyl phthalate, diethyl phthalate, butyl benzyl phthalate, tricresyl phosphate.

Applications

- Widely used in pharmaceutical formulations in sustained release application.
- Used in transdermal drug delivery systems
- Used in enteric film material

HYPROMELLOSE

Non proprietary names

BP : Hypermellose

JP : Hydroxypropyl methyl cellulose

Ph Eur : Hypromellosum

USP : Hypromellose

Synonyms:

Benecel MHPC, hydroxypropyl methyl ether,E464, hydroxypropyl methyl cellulose, HPMC, Methocel, methylcellulose, propylene glycol ether, methyl hydroxypropylcellulose, metalose, pharmacoat, spectracel 6, spectracel 15, Tylopur.

Chemical name:

Cellulose, 2-hydroxypropyl methyl ether.

Molecular weight : 10 000 – 1500 000

Functional category:

Coating agent, film former, rate controlling polymer for sustained release, stabilizing agent, suspending agent, tablet binder, viscosity- increasing agent.

Description

Hypermellose is an odourless and tasteless, white or creamy white fibrous or granular powder.

Typical properties

Acidity / alkalinity	**:** pH 5.5 – 8.0 for a 1% w/w aqueous solution.
Ash	**:** 1.5- 3.0% depending upon the grade.
Density	**:** 1.326 g/cm^3
Melting point	**:** browns at 190- 200^{0}c; chars at 225-230^{0}C
Glass transition temperature	**:** 170- 180^0 c.
Moisture content	**:** Hypermellose absorbs moisture from the atmosphere, the amount of water absorbed depending and relative humidity of the surrounding air.
Solubility	**:** Soluble in cold water, forming a viscous colloidal solution, practically insoluble in chloroform, ethanol(95%) and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol.
Specific gravity	**:** 1.26

Stability and storage conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at P^H 3-11. Increasing temperature reduces the viscosity of the solutions. Aqueous solutions are comparatively enzyme- resistant, providing good viscosity stability during long term storage. Hypermellose powder should be stored in a well- closed container, in a cool, dry place.

Incompatibilities

Hypermellose is incompatible with some oxidizing agents. Since it is nonionic, hypermellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

Safety

Hypermellose is widely used as excipient in oral and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products. Hypromellose is regarded as nontoxic and nonirritant material, although excessive oral consumption may have a laxative effect.

Applications

- It is widely used in oral and topical formulations, particularly ophthalmic formulations.
- It is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments.
- As a protective colloid , it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formulation of sediments.

- Hypermellose is also used in the manufacture of capsules, as an adhesive in plastic bandages, and as wetting agent for hard contact lenses. It is also widely used in cosmetics and food materials.

ETHYL CELLULOSE

Synonyms	**:**	aquacoat ECD, aqualon E 462, ethocel, surelease.
Chemical name	**:**	cellulose ethyl ether
Description	**:**	Ethylcellulose is a tasteless, free flowing, white to light tan-coloured powder.
Density	**:**	0.4 g/cm3
Glass transition temperature	**:**	129 – 133℃
Solubility	**:**	Ethyl cellulose is practically insoluble in glycerin, propylene glycol, water. Ethyl cellulose that contains less than 46.5% of ethoxy groups is freely soluble in chloroform. Methyl acetate, tetrahydrofuran, aromatic hydrocarbons and ethanol. Freely soluble in ethanol, ethyl acetate, methanol, toluene.
Specific gravity	**:**	1.12 – 1.15 g/cm3
Viscosity	**:**	5 – 100m pascals (7 – 100cp)
Functional category:		Coating agent, flavouring fixative, tablet binder, tablet filler, viscosity-increasing agent.

Stability and storage conditions:

Ethyl cellulose is stable, slightly hygroscopic material. Chemically resistant to alkali, more sensitive to acidic materials. Ethylcellulose is subjected to oxidative degradation in the presence of sunlight or UV light at elevated temperature. This may be prevented by use of antioxidant and chemical additives that absorb light in the 230-340nm range.

It should be stored at a temperature not exceeding 32ºC in a day area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Safety:

Ethyl cellulose widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethyl cellulose is not metabolized following oral consumption and is therefore a non-calorific substance. Because ethyl cellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

Ethyl cellulose generally regarded as a nontoxic non-allergenic and non irritating material. An ethyl cellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake.

Incompatibilities

With paraffin wax and microcrystalline wax.

Applications in pharmaceutical formulations:

- Hydrophobic coating agent for tablets and granules
- Modified the release of drug
- To mask the unpleasant taste of drug
- To improve the stability of formulation
- Thickness agent in creams, lotions, gels
- Used in cosmetics, food products.
- Binder in tablets.

LITERATURE REVIEW

Ubaidulla .U et al[19] (2007) prepared transdermal therapeutic system of carvedilol and the effect of hydrophilic and hydrophobic matrix on invitro and in vivo characteristics were studied. The patches made with polymers ethyl cellulose –poly vinyl pyrrolidone and eudragit RL- eudragit RS have great utility and use viable option for effective and controlled management of hypertension.

Gannu .R et al[20] (2007) developed nitrendipine transdermal patches and subjected to *in vitro* and *in vivo* characterization. Formulations composed of Eudragit RL100- HPMC combination and Eudragit RS100 and HPMC combination were prepared with 6% carvone as penetration enhancer and 15% propylene glycol as plasticizer. From the results it can be concluded that nitrendipine matrix type transdermal patches could be prepared with required flux having suitable mechanical properties.

Zhao .J.H et al[21] (2007) prepared a novel transdermal patch incorporating isosorbide di nitrate with bisoprolol. The *in vitro* and *in vivo* release profile showed that the combination therapy of nitrate and bisoprolol has shown benefits for treatment of hypertension than either drug alone.

Tanwar .Y.S. et al[22] (2007) studied on the development and evaluation of carvedilol transdermal patches. The patches of carvedilol with HPMC drug reservoir were prepared and membranes of ERL 100 and ERS 100 were cast to achieve controlled release. The effects of non-ionic surfactants tween 80 and span 80 on drug

permeation were studied. Span 80 exhibit more release enhancement compared to tween 80.

Mundargi .R.C. et al[23] (2007) studied the possibility of using xanthan films as a matrix system for transdermal delivery of atenolol. The *in vitro* release profile showed a fickian diffusion trend.

Saraf Swarnalatha et al[24] (2006) has compared the effect of permeation of timolol maleate using polymer hydroxypropyl methyl cellulose and ethyl cellulose combination and with polyvinyl alcohol. The studies concluded that reservoir followed zero order kinetics while matrix followed first order kinetics. In matrix type patch polyvinyl alcohol is more permeable.

Gupta .S.P and Jain .S.K[25] (2006) studied about the polymeric matrix system for TDDS of atenolol using different ratios of ethyl cellulose- HPMC and films were subjected to *in vivo* and *in vitro* studies. The drug release from the films was found to be fickian diffusion type and exhibiting linear relationship between drug release and square root of time. It could be conclude that the designed polymeric matrix of TDDS of atenolol could be used for effective and prolonged duration.

Rathore RPS et al[26] (2006) has developed transdermal matrix type patches of terbutaline sulphate using ethyl cellulose and PVP combination and cellulose acetate – PVP combination. The drug release from both the systems follows Higuchi kinetics and higher release rates and permeability was achieved with cellulose acetate-PVP patches than EC-PVP.

Gupta .S.P and Jain .S.K[27] (2005) studied the effective and controlled transdermal drug delivery of metoprolol tartarate with polymers Eudragit RL and HPMC. The system comprising ERS and HPMC in 40:60 ratio exhibited drug skin permeation 87.5mcg/h/cm. This transdermal system was evaluated for its *in vivo* performance studies and compared its drug plasma profile with those obtained with oral multiple doses of conventional tablets of metoprolol tartarate. The TDDS exhibited better and constant plasma profile as compared to oral administration.

Aquil .M et al[28] (2005) prepared transdermal drug delivery of labetolol hydrochloride and evaluated for *in vitro, ex vivo* and *in vivo* characteristics using ERS 100 –ERL 100 combination and ERL100 – PVP K 30 combination. The maximum drug release was observed in 24 hours.

Gupta .S.P and Jain .S.K[29] (September 2004) developed matrix membrane type transdermal drug delivery of atenolol using different combinations of polymers Eudragit RL with PVP and PEG400. These preparations were evaluated for *in vitro* studies and revealed that the designed polymeric matrix could be successful with improved performance.

Mutalik .S and Udupa .N[30] (March 2004) developed matrix type transdermal patches containing glibenclamide using different ratios of EC/PVP and ERL100 and ERS 100 by solvent evaporation technique. The pharmacokinetic evaluation showed that the patches could

maintain almost steady state concentration of drug within the pharmacologically effective range for prolonged period of time.

Narasimhamurthy .S and Shobha Rani .R Hiremath[31] (2001) studied the formulation and evaluation of controlled release transdermal patches of theophylline- salbutamol sulphate using HPMC as polymer. It was evident from the results that the formulation of TDDS for simultaneous delivery of theophylline and salbutamol is feasible and system is capable of maintaining therapeutic levels of drug in the blood.

Narasimhamurthy .S and Shobha Rani R. Hiremath[32] (March 21, 2001) studied the effect of physical and chemical permeation enhancers in transdermal delivery of terbutaline sulphate. Among the chemical permeation enhancers isopropyl myristate, tween80 and sodium lauryl sulphate, isopropyl myristate produced higher permeation. Magnetophoresis is used as physical enhancer. The presence of magnets on permeation of the drug was found to be similar to that of isopropyl myristate.

Kulkarni et al[33] (2000) studied the comparative evaluation of polymeric films for transdermal application. It includes the preparation and characterization of polymeric films of PVP, EC, ERS 100 and EVA. All the polymers used for the fabrication have good film forming properties , films were thin, flexible, smooth and transparent and films are permeable to drug and drug diffusion was extended over a longer period of time at a controlled state. Among the

4 films prepared EC films was found to be good with respect to drug diffusion.

Kanikkannan et al[34] (2000) studied on transdermal iontophoretic delivery of timolol maleate in albino rabbits. The use of transdermal iontophoresis is a promising technique for the systemic delivery of water soluble and ionic drugs of relatively large molecular size. The present study investiges the skin pretreatment with azone and iontophoresis on the pharmacodynamic effect of timolol maleate *in vivo* in rabbits. Iontophoresis in combination with azone can increase the transdermal; release of timolol maleate there by the required transport rate can be achieved by lower drug content.

Sridevi .S et al[35] (2000) developed acrylate based transdermal drug delivery for glibenclamide and evaluated its pharmacodynamic performance in male wister rats. The drug embedded in polymeric matrix of polymethacrylate and ethyl cellulose was evaluated for its hypoglycemic activity. TDDS significantly sustained the hypoglycemic activity for 24hours when compared to oral administration where the effect declined after 8 hours.

Oh .S.Y et al[36] (1999) studied the enhanced transdermal drug delivery of zidovudine using iontophoresis and penetration enhancers were compared. These enhancers worked synergistically with iontophoresis in the transdermal transport.

Jia-You Fang et al[37] (1999) studied transdermal iontophoretic delivery of diclofenac sodium from various polymers like PVP, HPMC, PVP-HPMC. The excised skin, human skin as well as

cellulose membranes were used to examine the *in vitro* drug permeation and microdialysis was used to monitor the drug concentration *in vivo.* They showed binary system having higher percentage than that of single polymer vehicle.

Rao .P.R and Diwan .P.V[38] (1998) studied the formulation and evaluation of polymeric films of diltiazem hydrochloride and indomethacin fabricated using ethyl cellulose – polyvinyl pyrrolidone films. The invitro skin permeation profiles showed increase of initial concentration of drugs in the films and also with the concentration of polyvinyl pyrrolidone.

Rama Rao et al .P[39] (1997) studied the influence of various permeation promoters on the *in vitro* percutaneous absorption of indomethacin. The enhancers used includes ethanol, PEG600, PG, oleic acid and IPM. The maximum solubility was observed in the system containing ethanol/oleic acid (50:50) and ethanol (40:60). Therefore permeation rate also increased in both cases. From these results it may be concluded that the incorporation of oleic acid to a co-solvent system of ethanol is very useful to improve the skin permeation rate of indomethacin.

Narasimhamurthy .S and Mini Satheesh[40] (1997) studied the enhancer synergism of propylene glycol in terbutaline sulphate in transdermal drug delivery systems. It was observed that transdermal permeability of terbutaline sulphate across the human skin was enhanced with the increasing plasticizer concentration.

Paranjothy .K.L.K and Thampi .P.P[41] (1997) developed transdermal patches of verapamil hydrochloride using sodium carboxy methyl guar as polymer matrix using propylene glycol as plasticizer and *in vitro* evaluation were done.

Bhatt .D.C et al[42] (1995) had formulated transdermal patches with matrix drug reservoir films using ethyl cellulose : polyvinyl pyrrolidone, Eudragit RL100: polyvinyl pyrrolidone, cellulose acetate butyrate : polyvinyl pyrrolidone. *In vitro* studies were done on ratskin and *in vivo* evaluation was done on dogs.

PURPOSE OF THE WORK

Systemic hypertension represents a significant risk factor for the development of atherosclerotic coronary artery disease and myocardial infraction, cerebro-vascular accidents and congestive heart failure. A major barrier for to the management of hypertension is the extent to which patients comply with treatment regimen

Metoprolol tartrate is a beta adrenoreceptor blocking agent used in the treatment of cardiovascular disorders. The drug has a short half-life of 3-4 hours and is reported to show extensive first pass metabolism following oral administration resulting in poor bioavailability. Long term therapy of hypertension using metoprolol tartarate orally may result in poor patient compliance because of low bioavailability and short plasma half-life. This problem of the drug metoprolol tartrate can be minimized by the formulation of the transdermal delivery system. Transdermally delivered drug provides the patients a unique and convenient dosing schedule while providing nearly constant serum levels of medication over a prolonged period. The minimum concentration needed to produce the effective therapeutic concentration for metoprolol tartrate is in the range of 20-100ng/ml.[43]

The ideal requirement of metoprolol tartrate with respect to its solubility, molecular weight, melting point, bioavailability and half-life etc for its incorporation into matrix type. Polymeric films of transdermal delivery system prompted the selection of metoprolol for this study.

PLAN OF THE WORK

The present work is undertaken to prepare and evaluate a transdermal delivery system for the drug metoprolol tartrate. It was planned to carry out this work as outlined below.

- Solubility and compatibility studies for selection of polymers used for film casting.
- Casting of plain films.
- Preparation of drug incorporated polymeric films (matrix type using polymers CAB, PVP, HPMC and EC in different ratios)
- Evaluation of patches for physicochemical characteristics.

Physical characteristics

- Moisture content
- Moisture uptake
- Weight variation
- Drug content
- Film thickness
- Tensile strength
- Skin irritation test

***In vitro* release studies**

Drug stability

MATERIALS AND EQUIPMENTS

Table 2 Materials used

Materials	Company
Metoprolol tartrate	Gift from Astrazeneca
Cellulose acetate butyrate	Glaxo (Kemphasol)
Poly vinyl pyrrolidone	Loba Chemicals
Hydroxyl propyl methyl cellulose	High media
Ethyl cellulose	Kemphasol
Di n-butyl phthalate	Ranbaxy
Isopropyl myristate	Sd Fine Chemicals
Potassium dihydrogen phosphate	Fischer Inorganic & Aromatic Ltd
Methanol	Sd Fine Chem.
Chloroform	Quligens Fine Chemicals
Ethanol	Commercial Alcohol Inc
Aluminium foil	Sd Fine Chemicals Ltd
Syringe 5 ml	Core Pharmaceuticals
Ammonia	Sd Fine Chem.
Calcium chloride	Sd Fine Chem.
Potassium chloride	Sd Fine Chem.
Cellulose membrane (0.2µ)	Sartorius
Mercury	Ranbaxy

Table 3: Equipments used

Franz diffusion cell	Fabricated
UV- visible spectrophotometer	Jasco V-530
FT-IR spectrophotometer	Jasco-410
Digital balance	Denver Instrument
Hot air oven	Lab Equipment Pvt Ltd
Magnetic stirrer	Remi Motors
Circulating water bath	From Dissolution Apparatus
Circular mould disc	Fabricated
Vacuum desicator	Tarrsons
Micropipette	Electro Lab
Dissolution apparatus	High Tech Labs

EXPERIMENTAL WORK

Standard graph of metoprolol tartrate[44]

Preparation of stock solution

10 mg of metoprolol tartrate was dissolved in methanol and made upto 100 ml to obtain 100mcg/ml working standard.

Calibration graph of metoprolol tartrate

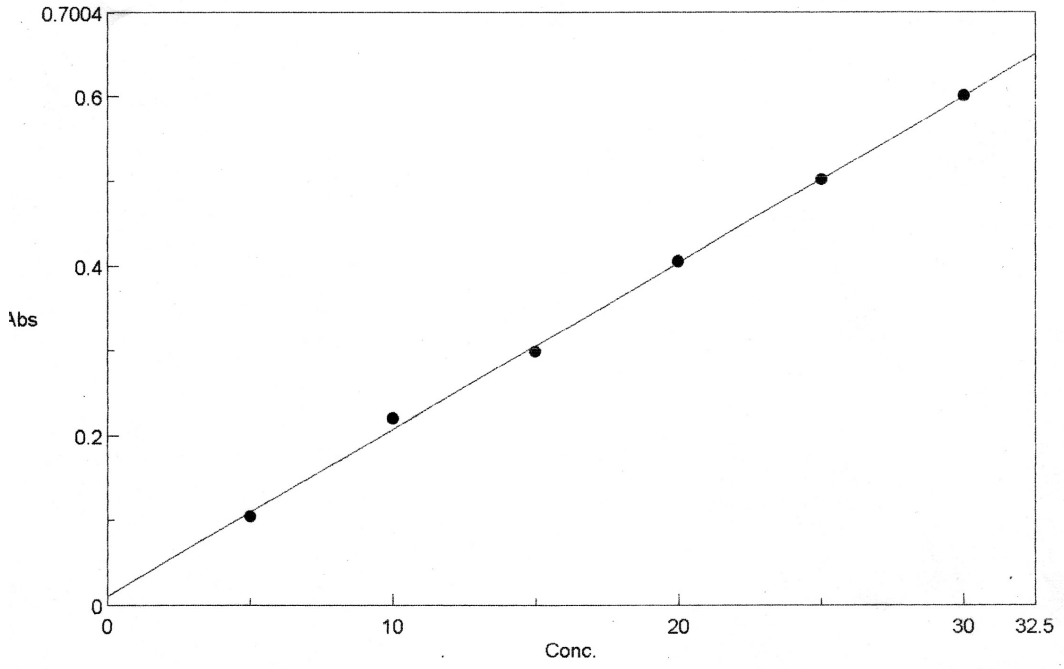
Aliquots of 0.5 ml to 3.0 ml portions representing 5 to 30 mcg of drug were transferred to different 10 ml volumetric flask. To each flask methanol is added and made up to 10 ml. Then absorbance was measured at 225 nm against a blank solution prepared in similar manner without the addition of drug.

Table 4 : Data of absorbances of standard graph

Sl. No.	Concentration in mcg/ml	Absorbance at 225 nm
1	5	0.104
2	10	0.201
3	15	0.296
4	20	0.405
5	25	0.492
6	30	0.581

Fig 4

Calibration curve of metoprolol tartrate



No. of WL: 1-WL method
Peak : 225.0 nm
Response: Quick
BandWidth: 2.0 nm
No. of cycles: 1

Calib Curve: Linear
Expression: Abs = A + B * Conc
Factor: A = 0.0115
B = 0.0196
Coefficient: 0.999312

Standard blank: 0.0000
Blank correct: Off

DEVELOPMENT OF PATCHES

In the present study matrix type transdermal patches of metoprolol tartrate were prepared by mercury substrate method. A flat circular glass mould was fabricated for this purpose. The transdermal patches were prepared using polymers in different ratios.

Three types of polymeric patches were prepared using polymer combinations. It includes

Cellulose acetate butyrate – polyvinyl pyrrolidone

Ethyl cellulose- hydroxyl propyl methyl cellulose

Ethyl cellulose- Polyvinyl pyrrolidone

CAB and PVP patches were prepared by dissolving CAB in measured volume of chloroform and kept aside for 4 hours to facilitate the polymer to dissolve in the solvent. Then add specified quantities of PVP, DBP and isopropyl myristate as listed in table.5

The polymeric solution of EC and HPMC were prepared by dissolving separately in methanol- chloroform (1:1) mixture. Both solutions are mixed in different ratios using dibutyl phthalate as plasticizer. The polymeric solution of EC and PVP were prepared by dissolving in chloroform in different ratios.

A weighed amount of drug is dissolved in suitable solvent and dispersed in polymer mixture and this solvent is poured in to the ring placed on mercury surface in a Petri dish and solvent evaporation was controlled by covering with a funnel. After 24 hours the patches were removed and kept in dessicator to remove any adhering solvents, the films were cut in circular disc with 3.8cm diameter. These patches were wrapped in aluminium foil, packed in self sealing cover and kept in dessicator.

Table: 5 : composition of transdermal patches

Formulation	MT in mg	CAB in parts	PVP in parts	EC in parts	HPMC in parts	DBP in % W/W	IPM in % W/W
F_1	15	4.5	0.5			30	20
F_2	15	4.0	1.0			30	20
F_3	15	3.5	1.5			30	20
F_4	15	3.0	2.0			30	20
F_5	15	2.5	2.5			30	20
F_6	15	2.0	3.0			30	20
F_7	15	1.5	3.5			30	20
F_8	15			4.5	0.5	30	20
F_9	15			4.0	1.0	30	20
F_{10}	15			3.5	1.5	30	20
F_{11}	15			3.0	2.0	30	20
F_{12}	15			2.5	2.5	30	20
F_{13}	15			2.0	3.0	30	20
F_{14}	15			1.5	3.5	30	20
F_{15}	15		0.5	4.5		30	20
F_{16}	15		1.0	4.0		30	20
F_{17}	15		1.5	3.5		30	20
F_{18}	15		2.0	3.0		30	20
F_{19}	15		2.5	2.5		30	20

EVALUATION OF TRANSDERMAL PATCHES

The prepared patches were evaluated for their physico-chemical parameters, *in vitro* diffusion studies, skin irritation and stability studies.

Physicochemical parameters

1. Weight variation

As weight variation between the formulated patches can lead to difference in drug content and *in vitro* behaviour, a study was carried out weighing 5 patches in an electronic balance. The average weight of a patch and its standard deviation was calculated by using the following formulae.

Average weight of each patches = total weight of 5 patches/5

$$\text{Standard deviation} = \sqrt{\frac{\sum (x-X)^2}{n-1}}$$

Where x = weight of individual patch

X = average weight

n = number of patches

2. Percentage of moisture content

The films were weighed individually and kept in a dessicator containing anhydrous calcium chloride at room temperature for 24 hours. Individual films were weighed repeatedly until they showed a constant weight. The percentage of moisture content was calculated as the difference between initial and final weight with respect to the final weight.

3. Percentage moisture uptake

Moisture uptake can influence the mechanical strength and drug release of the transdermal therapeutic system. It was done by weighing the film and keeping in a dessicator at room temperature for 24 hours and patches were removed and exposed to 84% relative humidity(a saturated solution of potassium chloride) in a dessicator until a constant weight for the film was obtained. The percentage of moisture uptake was calculated as difference between final weight and initial weight with respect to final weight.

$$\text{Percentage moisture uptake} = \frac{\text{final weight- initial weight}}{\text{final weight}} \times 100$$

4. Drug content

A film was cut into small pieces, put into a 100ml buffer (PH-7.4) and shaken continuously for 24 hours. Then the solution was filtered. After filtration, the drug content was estimated at wave length 225nm.

5. Film thickness

The thickness was measured at 5 different places for 5 films using a dial caliper and mean value were calculated.

6.Tensile Strength

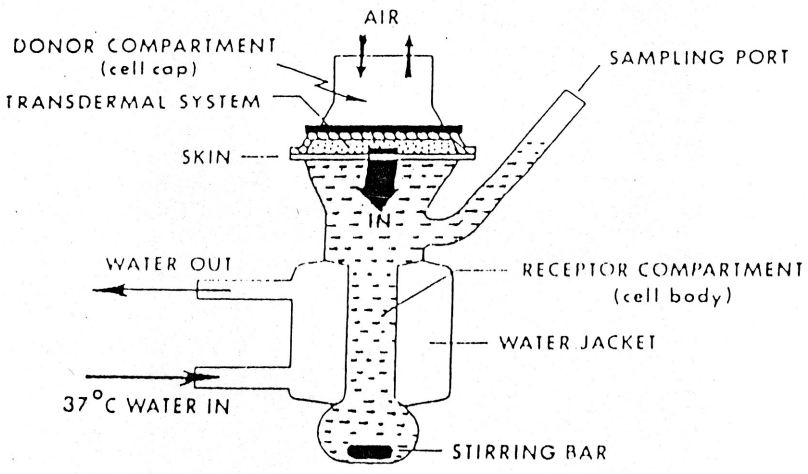
It was determined by using a modified pulley system. Weight was gradually increased so as to increase the pulley force till the patch broke. The percentage elongation before the patch broke was noted with the help of a magnifying glass on a graph paper and the tensile strength was calculated as kg/mm^2.

***In vitro* permeation studies**

In vitro permeation studies were performed using Franz diffusion cell. It consists of a donor compartment and a receptor compartment. The cellulose membrane[45] was mounted between the donor compartment and receptor compartment of the diffusion cell. The formulated patches were placed over the membrane. The receptor compartment of the diffusion cell was filled with phosphate buffer pH 7.4. The whole assembly was fixed on a magnetic stirrer, and the solution in the receptor compartment was constantly and continuously stirred using magnetic bead at 50 rpm; the temperature was maintained at 37 ± 1^0C. The samples were withdrawn at different time intervals and analysed for drug content. The receptor phase was replenished with an equal volume of phosphate buffer at each sample withdrawal. The cumulative amount of drug permeated/cm^2 of patches were plotted against time.

Fig 5

Franz Diffusion Apparatus



Skin irritation studies

Patches were applied to the depilated skin of the back of two rabbits and secured using an adhesive tape. On one side blank patches were applied and on other side experimental patches were secured. The animals were observed for any signs of erythemia or edema for a period of 48 hours.

Accelerated Stability Studies

To any rational design and evaluation of dosage forms, the stability of the active component in the formulation must be major criteria in determining their acceptance or rejection. The drugs instability by a physical appearance, colour, odour, taste or texture of the formulation. Scientific data pertaining to the stability of a formulation leads to the prediction of the expected shelf life of the product and if necessary reformulation of the dosage form can be done.

Hence to determine the shelf life, formulations F_7, F_{14}, F_{19} were selected and stored at temperatures 25^0C and 37^0C for 30 days. The patches were evaluated for physico-chemical properties and their drug content and *in vitro* release in 10 days interval.

RESULTS AND DISCUSSION

Compatibility studies

IR

The presence of all characteristic peaks of metoprolol tartrate, in IR spectra obtained with metoprolol tartrate and the other excipients confirms the intactness of the drug in the polymer matrix.(fig.11,12 and 13).

Thin layer chromatography: (TLC)

A thin layer chromatographic method was also carried to study the interaction between the drug and the polymer. A single distinct spot at the same height for both drug and formulation was having the same R_f value of 0.428 confirms the intactness of the drug in the polymer matrix.

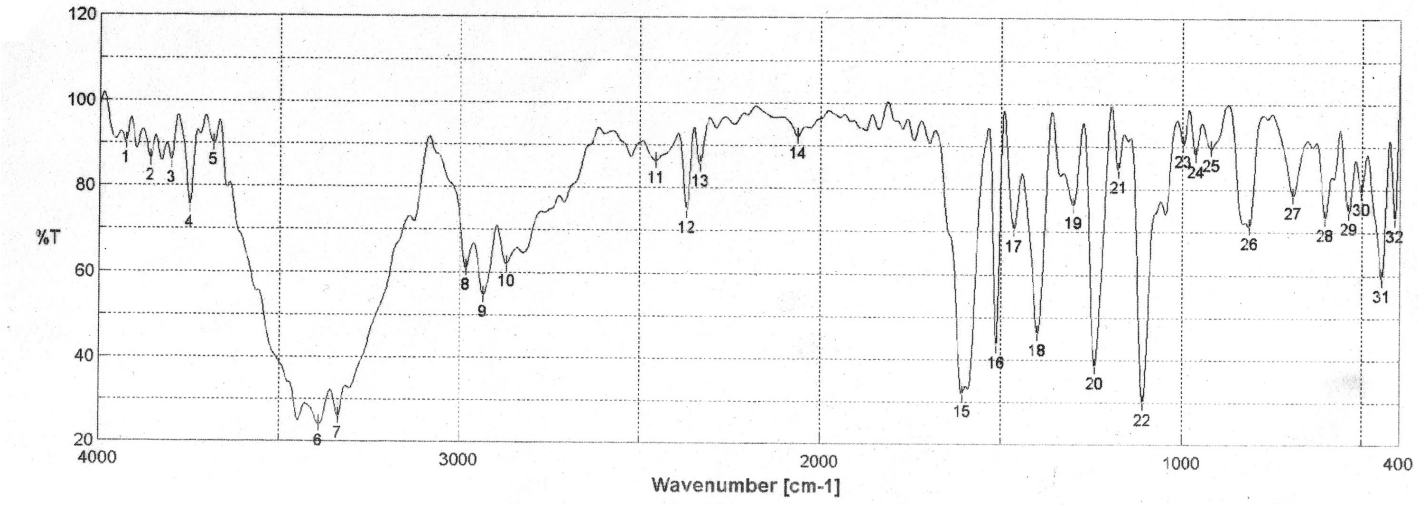
The TLC system used for this study is given below.

Pre-coated TLC Plates	: Manufactured by SD Fine chemicals Ltd, Mumbai
Adsorbent Layer	: Silicagel GF254.
Layer Thickness	: 250 µm.
Separation technique	: Ascending
Chamber Saturation	: The chamber was lined on three sides with filter paper and saturated for 30 minutes.
Mobile phase	: Chloroform : Methanol: Ammonia (9 : 1 : .0.05)

Preparation of sample	: A suitable amount of pure drug or equivalent solid dispersion was dissolved in ethanol and used for spotting
Amount applied	: 10 µl
Detection	: Short and long wavelength of light

Fig 6

IR SPECTRUM METOPROLOL TARTRATE (Obtained Sample)

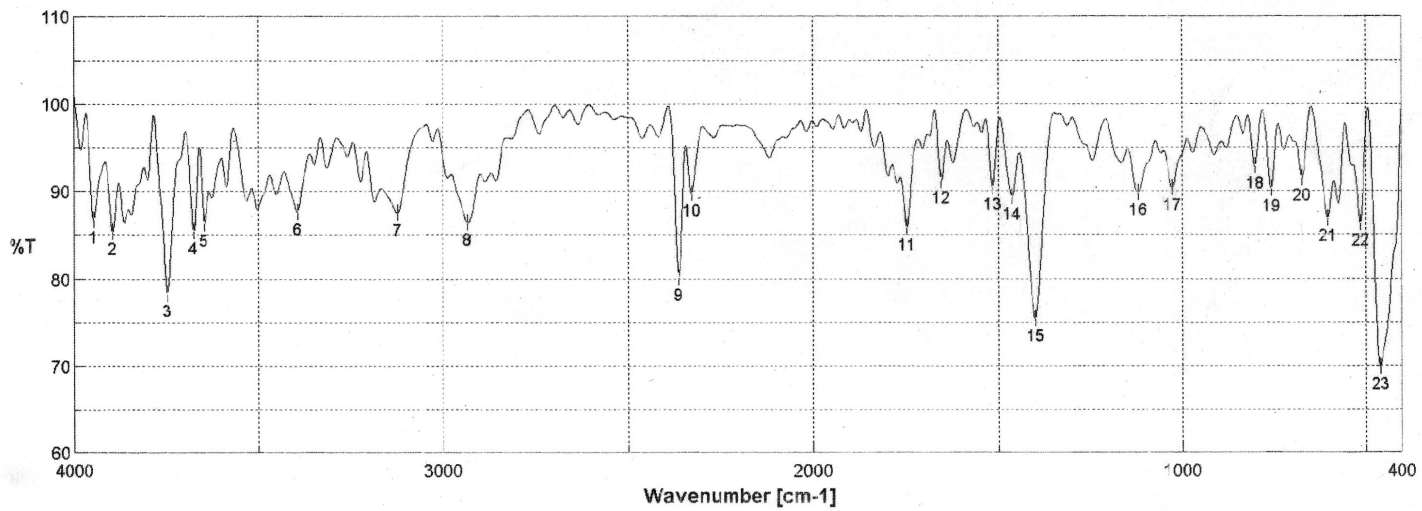


Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 11:09AM	Update	12/13/2007 10:19AM
Operator	C.Geetha		
File Name	METOPROLOL -T		
Sample Name	METOPROLOL -T		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3930.22	90.3483	2	3860.79	86.3285	3	3801.01	85.8663	4	3747.98	75.5193	5	3680.48	90.095
6	3389.28	24.1607	7	3335.28	26.1094	8	2983.34	60.9898	9	2934.16	54.73	10	2868.59	62.0044
11	2454.94	86.3524	12	2367.19	74.7766	13	2331.52	85.6483	14	2065.39	92.2274	15	1608.34	31.9074
16	1512.88	43.3824	17	1462.74	70.5919	18	1396.21	46.1846	19	1301.72	76.2782	20	1242.9	38.5666
21	1179.26	84.5761	22	1109.83	29.97	23	996.053	90.5211	24	962.305	88.2043	25	919.879	89.7189
26	816.706	71.3034	27	693.284	78.6809	28	602.646	73.5114	29	536.114	74.9237	30	502.366	79.5776
31	447.404	59.1737	32	412.692	73.2234									

Fig 7

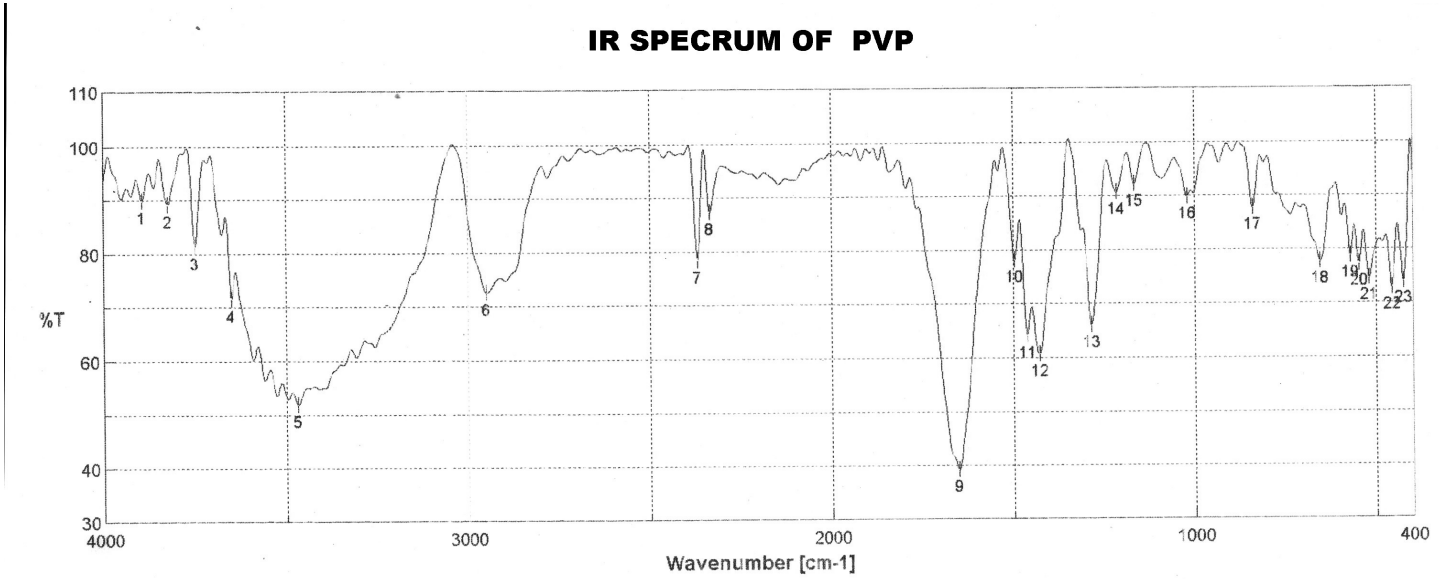
IR SPECTRUM OF CAB



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 11:26AM	Update	12/13/2007 10:12AM
Operator	C.Geetha		
File Name	CAB		
Sample Name	CAB		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3945.64	86.6841	2	3893.57	85.3752	3	3747.98	78.3224	4	3676.62	85.5166	5	3647.7	86.3854
6	3395.07	87.6583	7	3125.08	87.5017	8	2933.2	86.4288	9	2367.19	80.1703	10	2333.44	89.7441
11	1746.23	85.9055	12	1650.77	91.1948	13	1514.81	90.4943	14	1462.74	89.3679	15	1400.07	75.396
16	1117.55	89.8477	17	1025.94	90.3724	18	796.457	92.9464	19	752.102	90.3512	20	671.106	91.5352
21	603.61	86.9183	22	514.901	86.2994	23	459.939	69.8596						

Fig 8

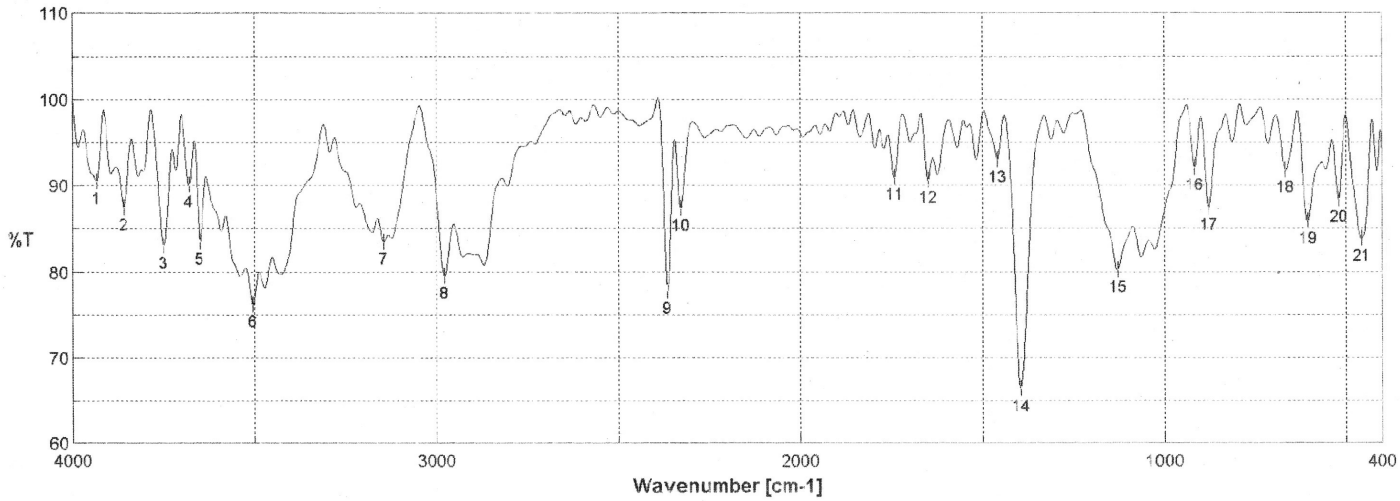


Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 11:34AM	Update	12/13/2007 10:10AM
Operator	C.Geetha		
File Name	PVP		
Sample Name	PVP		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3893.57	89.901	2	3822.22	89.2008	3	3747.01	81.3023	4	3647.7	71.6111	5	3468.35	51.8504
6	2948.63	72.5153	7	2367.19	78.3262	8	2334.41	87.3916	9	1655.59	39.2726	10	1496.49	78.152
11	1461.78	64.162	12	1428.99	60.7576	13	1289.18	66.0122	14	1218.79	90.715	15	1166.72	92.2195
16	1019.19	89.8619	17	842.74	87.8172	18	653.75	77.7184	19	569.862	78.7895	20	545.756	77.3822
21	518.758	74.6036	22	458.011	72.8313	23	426.191	74.0797						

Fig 9

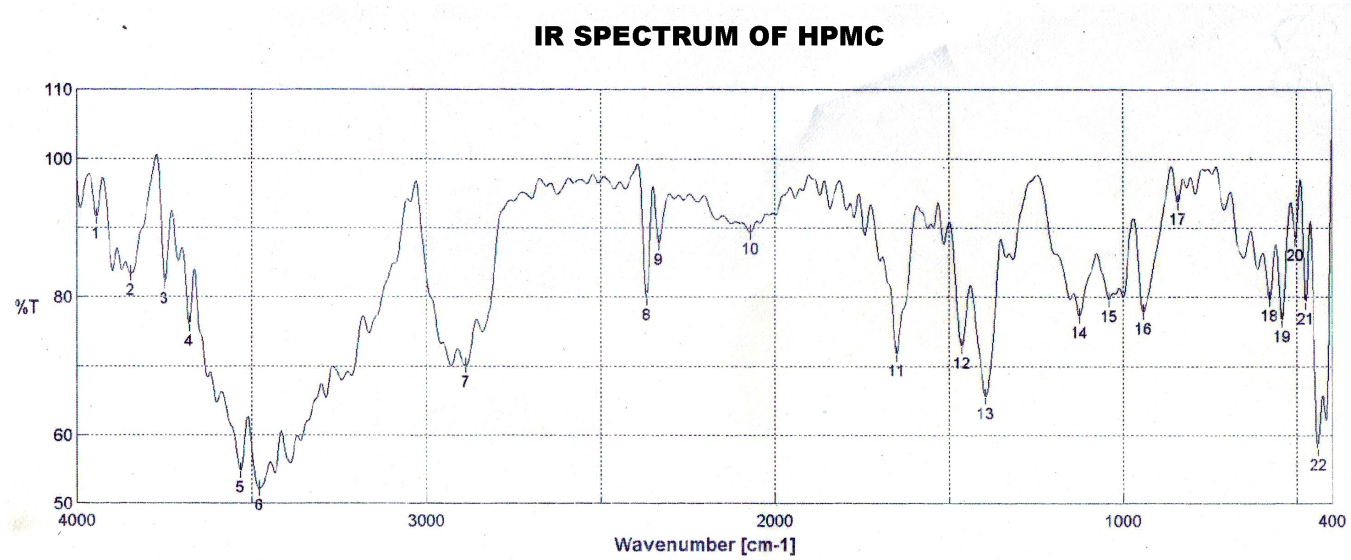
IR SPECTRUM OF EC



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	4	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 11:49AM	Update	12/13/2007 10:14AM
Operator	C.Geetha		
File Name	EC		
Sample Name	EC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3934.07	90.5359	2	3857.9	87.4724	3	3747.01	83.0295	4	3677.59	90.0865	5	3647.7	83.5134
6	3504.02	76.1317	7	3146.29	83.4364	8	2977.55	79.4599	9	2367.19	77.769	10	2332.48	87.3526
11	1745.26	90.9264	12	1649.8	90.5942	13	1459.85	93.0077	14	1398.14	66.3897	15	1126.22	80.2315
16	916.986	92.1137	17	877.452	87.404	18	662.428	91.765	19	601.682	85.8519	20	519.722	88.3344
21	458.011	83.8164												

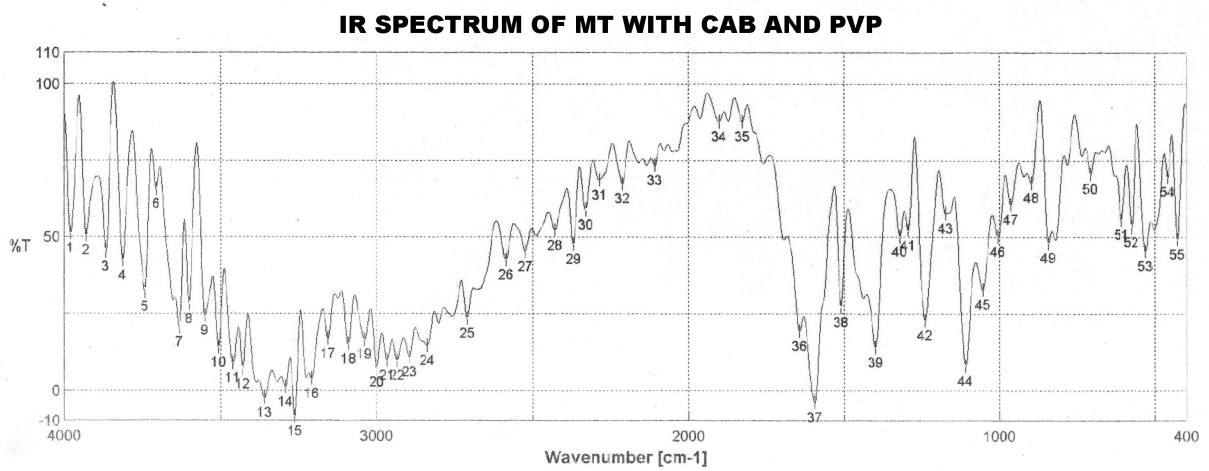
Fig 10



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	8	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 11:56AM	Update	12/13/2007 10:18AM
Operator	C.Geetha		
File Name	HPMC		
Sample Name	HPMC		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3944.68	91.5564	2	3847.29	83.4154	3	3747.01	82.1501	4	3675.66	76.1111	5	3531.02	54.8169
6	3477.99	52.2028	7	2885.95	70.0278	8	2369.12	79.8545	9	2334.41	87.8272	10	2072.14	89.4031
11	1650.77	71.7514	12	1462.74	72.8652	13	1396.21	65.5615	14	1125.26	77.2648	15	1039.44	79.6495
16	942.056	77.8687	17	842.74	93.745	18	576.612	79.7081	19	540.935	76.7366	20	503.33	88.4901
21	474.403	79.2732	22	440.655	58.1072									

Fig 11

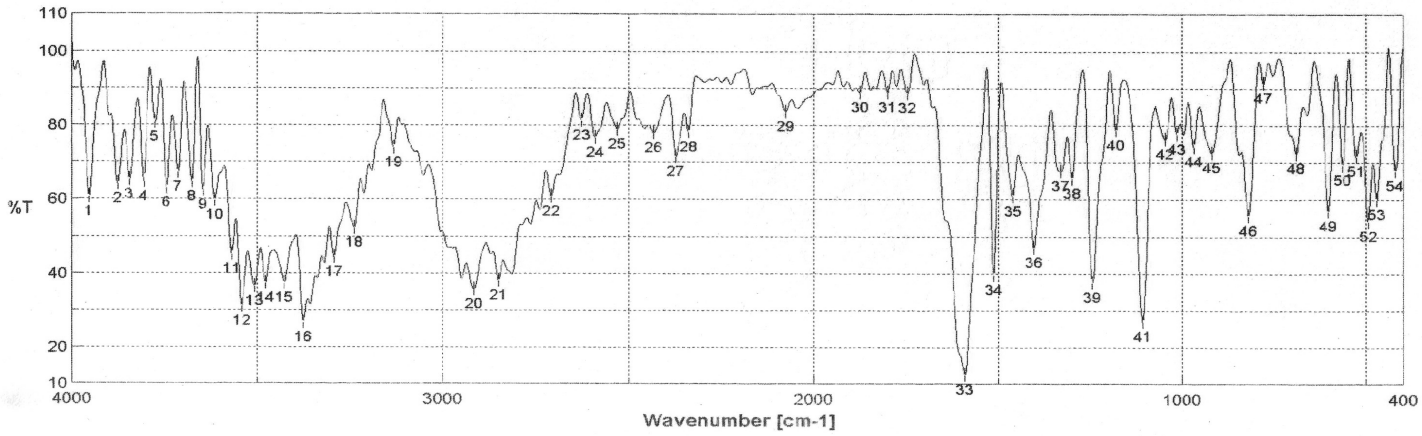


Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	64	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 0:06PM	Update	12/13/2007 10:21AM
Operator	C.Geetha		
File Name	Mix 1		
Sample Name	Mix 1		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3980.36	51.2415	2	3931.18	50.5825	3	3868.5	45.151	4	3814.51	42.2989	5	3742.19	32.2262
6	3704.58	65.5713	7	3629.37	20.6539	8	3598.52	28.1921	9	3549.34	24.3832	10	3506.92	13.9322
11	3461.6	8.76996	12	3430.74	6.93704	13	3360.35	-2.46769	14	3292.86	0.991175	15	3261.04	-8.43641
16	3206.08	3.75238	17	3153.04	16.7405	18	3089.4	15.0077	19	3039.26	16.5795	20	3000.69	7.46602
21	2966.95	9.82008	22	2934.16	9.78509	23	2894.63	10.7642	24	2836.77	14.6525	25	2709.5	23.5607
26	2588	42.6736	27	2525.33	45.1516	28	2429.87	52.0849	29	2371.05	47.6427	30	2331.52	58.8421
31	2287.16	68.5526	32	2212.92	67.3971	33	2109.74	73.3406	34	1902.43	87.6356	35	1827.22	87.5663
36	1644.98	19.1794	37	1595.81	-4.05592	38	1509.99	27.0838	39	1397.17	13.988	40	1320.04	50.1976
41	1293.04	52.2102	42	1240	22.8495	43	1173.47	57.5631	44	1108.87	8.05071	45	1052.94	32.7718
46	1002.8	50.1239	47	961.341	60.4662	48	895.773	67.6518	49	841.776	48.1283	50	708.712	70.5378
51	608.431	55.577	52	573.719	53.2023	53	527.436	45.5002	54	458.975	69.5929	55	428.12	49.303

Fig 12

IR SPECTRUM OF MT WITH EC AND HPMC

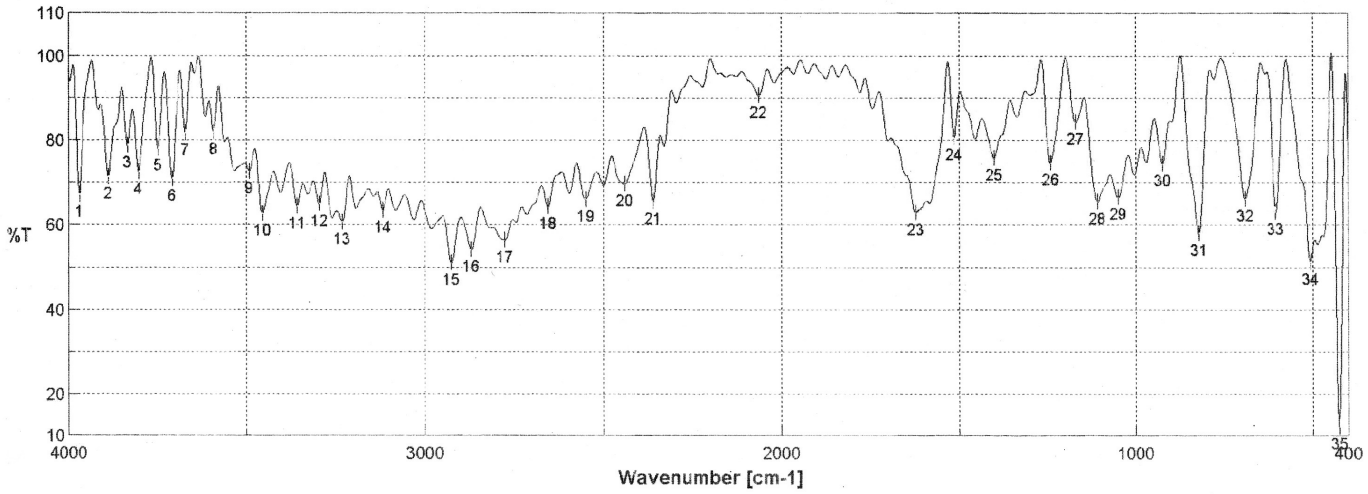


Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 0:13PM	Update	12/13/2007 10:23AM
Operator	C.Geetha		
File Name	Mix 2		
Sample Name	Mix 2		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3953.36	60.6756	2	3879.11	64.1063	3	3847.29	65.2125	4	3808.72	64.6627	5	3777.87	80.7682
6	3746.05	63.0119	7	3714.23	67.3633	8	3675.66	64.7757	9	3644.8	62.4353	10	3612.98	59.7645
11	3567.66	45.1815	12	3539.7	31.0638	13	3506.92	36.4613	14	3477.99	37.4304	15	3428.81	37.4263
16	3378.67	26.6334	17	3294.79	44.3433	18	3239.82	52.4017	19	3131.83	74.035	20	2916.81	35.6969
21	2850.27	38.1817	22	2706.6	60.835	23	2625.61	81.4029	24	2589.93	76.8141	25	2531.11	78.9706
26	2433.73	77.9839	27	2373.94	71.582	28	2340.19	78.2197	29	2075.99	83.7673	30	1873.51	88.9423
31	1797.33	88.8691	32	1744.3	88.7209	33	1590.99	12.5751	34	1512.88	39.5819	35	1459.85	60.7647
36	1401.03	46.8933	37	1327.75	67.6159	38	1297.86	65.5942	39	1243.86	37.5135	40	1181.19	78.6752
41	1107.9	27.0125	42	1045.23	76.3381	43	1013.41	77.7111	44	967.126	74.2894	45	917.95	72.6631
46	820.563	55.7383	47	780.065	91.4411	48	691.355	72.437	49	602.646	56.8978	50	563.112	69.2635
51	526.471	71.6944	52	493.688	54.2148	53	470.546	60.0626	54	421.37	67.8395			

FIG 13

IR SPECTRUM OF MT WITH EC AND PVP



Accumulation	16	Resolution	4 cm-1
Zero Filling	ON	Apodization	Cosine
Gain	32	Scanning Speed	2 mm/sec
Date/Time	11/29/2007 0:19PM	Update	12/13/2007 10:25AM
Operator	C.Geetha		
File Name	Mix 3		
Sample Name	Mix 3		
Comment			

No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T	No.	cm-1	%T
1	3968.78	67.0927	2	3889.72	71.4334	3	3836.68	78.7288	4	3805.83	72.4754	5	3750.87	78.0107
6	3711.33	70.7247	7	3673.73	81.7535	8	3591.77	81.9878	9	3491.49	72.6099	10	3455.81	62.7544
11	3361.32	64.4079	12	3299.61	64.9333	13	3235	60.6887	14	3117.37	63.4261	15	2927.41	50.9898
16	2871.49	54.1579	17	2776.99	56.4687	18	2653.57	64.2753	19	2550.4	65.9932	20	2443.37	69.6298
21	2363.34	65.3943	22	2064.42	90.5999	23	1622.8	62.901	24	1513.85	80.6091	25	1399.1	75.8102
26	1240.97	74.6237	27	1171.54	84.3665	28	1108.87	65.3778	29	1050.05	66.527	30	921.807	74.4533
31	820.563	58.0264	32	692.32	66.1688	33	604.574	63.1207	34	506.223	51.1961	35	425.227	12.2001

FORMULATION AND *IN VITRO* EVALUATION

Total 19 patches were prepared. In this the first 7 patches (F_1 – F_7) contained the polymers CAB & PVP. The next 7 patches (F_8-F_{14}) were prepared using EC & HPMC in varying concentration. The last 5 patches (F_{15}-F_{19}) prepared using EC& PVP. All the 19 patches were evaluated for physical appearance, moisture content, moisture uptake, weight variation, drug content, thickness and tensile strength.The values are represented in table 6, 7 and 8.

Physical Appearance

The physical appearance for the patches F_1-F_7 was found to be transparent, smooth and flexible. The next patches F_8-F_{14} were translucent, moist and flexible. The last patches F_{15}-F_{19} was found to be translucent, smooth and flexible.

Moisture Content & Moisture Uptake

All the 19 patches (F_1- F_{19}) the percentage moisture content and moisture uptake was found to increase with increase in the PVP concentration.

Weight variation

Out of 19 patches; formulations containing EC & HPMC in varying concentration showed an increase in weight compared to the other two batches containing CAB&PVP and EC& PVP.

Drug content

Drug content in all the batches were found to be similar with minor variations. The CAB- PVP patch showed maximum drug content.

Film thickness

Out of 19 patches; formulations containing EC & HPMC in varying concentration showed an increase in thickness compared to the other two batches containing CAB & PVP and EC & PVP.

Tensile Strength

The tensile Strength of CAB- PVP patches were found to be more when compared to EC - HPMC and EC - PVP Patches.

Table 6 Physico–chemical properties of the prepared transdermal patches of MT

Patch no	Physical appearance	Percentage Moisture content(±SD)	Percentage Moisture uptake(±SD)	Weight variation in mg (±SD)	Drug content in mg(±SD)	Film thickness in µg/cm^2(±SD)	Tensile Strength in kg/ mm^2
F_1	Transparent, flexible and smooth	4.94±2.18	5.06±3.77	107.43±0.78	0.9838±0.8	0.138±1.44	1.81±3.27
F_2	Transparent, flexible and smooth	5.39 ±2.71	6.65 ±5.14	110.62±0.33	0.9846±1.7	0.136±1.36	1.76±2.65
F_3	Transparent, flexible and smooth	7.21 ±3.22	7.85 ±4.27	114.21±0.39	0.9896±0.6	0.132±2.24	1.28±3.69
F_4	Transparent, flexible and smooth	8.52±3.81	8.74 ±2.84	117.33±0.72	1.0022±0.36	0.141±1.28	1.42±4.15
F_5	Transparent, flexible and smooth	9.14 ±3.64	9.79 ±3.91	122.57±0.68	1.0080±1.1	0.135±2.12	1.69±2.41
F_6	Transparent, flexible and smooth	9.52±5.24	10.23±4.81	124.12±0.82	1.018±0.22	0.138±1.45	1.34±1.15
F_7	Transparent, flexible and smooth	10.11 ±5.19	11.47 ±3.21	127.45±0.42	1.030±0.52	0.134±1.54	1.53±2.67

n=5

Table 7 Physico–chemical properties of the prepared transdermal patches of MT

Patch no	Physical appearance	Percentage Moisture content (±SD)	Percentage Moisture uptake (±SD)	Weight variation in mg (±SD)	Drug content in mg/cm^2 (±SD)	Film thickness in µm	Tensile Strength in kg/ mm^2
F_8	Translucent, flexible, smooth.	3.91±1.14	4.11±2.71	117.14±0.22	0.9821±1.2	182±2.14	1.32±1.68
F_9	Translucent, flexible, smooth.	5.37±2.37	5.35±1.77	121.37±0.24	0.9888±0.79	186±1.54	1.36±2.15
F_{10}	Translucent, flexible, smooth.	6.91±3.27	7.05 ± 3.12	123.44±0.51	0.9924±0.48	179±2.6	1.04±3.39
F_{11}	Translucent, flexible, smooth.	7.64±4.22	7.75 ±3.49	126.69±0.82	1.0031±0.52	184±1.58	1.12±2.42
F_{12}	Translucent, flexible, smooth.	8.27±3.51	8.37±2.18	131.62±0.39	1.004±0.12	178±1.76	1.07±1.63
F_{13}	Translucent, flexible, smooth.	8.64±2.54	9.25 ±2.19	134.58±0.71	1.015±1.82	181±1.42	1.18±3.71
F_{14}	Translucent, flexible, smooth.	9.59±4.87	10.46±3.21	137.23±0.42	1.029±0.84	176±1.45	1.24±3.67

n=5

Table 8 Physico–chemical properties of the prepared transdermal patches of MT

Patch no	Physical appearance	Percentage Moisture content (±SD)	Percentage Moisture uptake (±SD)	Weight variation in mg(±SD)	Drug content in mg/cm^2 (±SD)	Film thickness in µm	Tensile Strength in kg/ mm^2
F_{15}	Translucent, flexible, smooth.	3.24±2.22	4.03±2.24	112.31±0.26	0.9084±1.32	152±1.22	1.13±2.14
F_{16}	Translucent, flexible, smooth.	5.12±3.17	5.37± 3.32	114.98 ±0.34	0.9184±0.72	145±1.46	0.981±3.51
F_{17}	Translucent, flexible, smooth.	6.29±4.24	6.88 ±3.56	119.27± 0.41	0.9260±0.39	157±2.12	0.996±2.69
F_{18}	Translucent, flexible, smooth.	7.18±4.37	7.60±2.38	121.36 ±0.65	0.9762±0.72	153±1.68	0.957±1.59
F_{19}	Translucent, flexible, smooth.	7.92±3.96	8.08 ±2.68	124.47 ±0.81	0.9829±0.54	148±2.24	0.923±3.73

n= 5

***In vitro* release**

Formulations F_1-F_7 containing CAB-PVP in the ratios 9:1,8:2,7:3, 6:4, 5:5, 4:6 and 3:7 showed a steady increase in the release with increase in time. Similarly formulations F_8-F_{14} and F_{15} – F_{19} also showed a steady increase in release with time. Out of all the patches the patch containing CAB- PVP in the ratio 3:7 showed better release characteristics. The cumulative release of metoprolol tartrate released from three polymeric films in 24 hours was found to be between 42.9% to 49.2%.

Table 9 Cumulative percentage released for the patches F_1, F_8 and F_{15}

Time	F_1CAB-PVP 9:1		F_8 EC- HPMC 9:1		F_{15} EC-PVP 9:1	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	15.61±3.64	1.586	12.45±4.68	1.259	10.52±4.38	1.158
2	44.33±2.46	4.505	37.57±3.35	3.83	16.54±4.29	1.820
3	74.27±2.95	7.549	47.91±4.87	4.98	26.22±5.92	2.886
4	91.57±5.23	9.307	71.37±3.11	7.267	49.79±3.12	5.481
5	117.61±4.35	11.95	96.18±2.41	9.79	69.54±2.82	7.655
6	142.13±3.27	14.44	112.45±3.55	11.449	87.36±1.98	9.616
7	161.87±4.48	16.45	132.39±5.82	13.48	107.54±4.76	11.838
8	183.38±3.18	18.639	148.73±2.55	15.144	132.67±4.14	14.604
9	199.78±4.13	20.306	174.92±3.71	17.810	162.45±3.29	17.883
10	211.62±4.77	21.510	198.33±4.79	20.194	195.49±2.13	21.499
24	441.32±2.95	44.85	419.74±3.47	42.73	381.12±2.16	41.955

n = 3

Fig 14

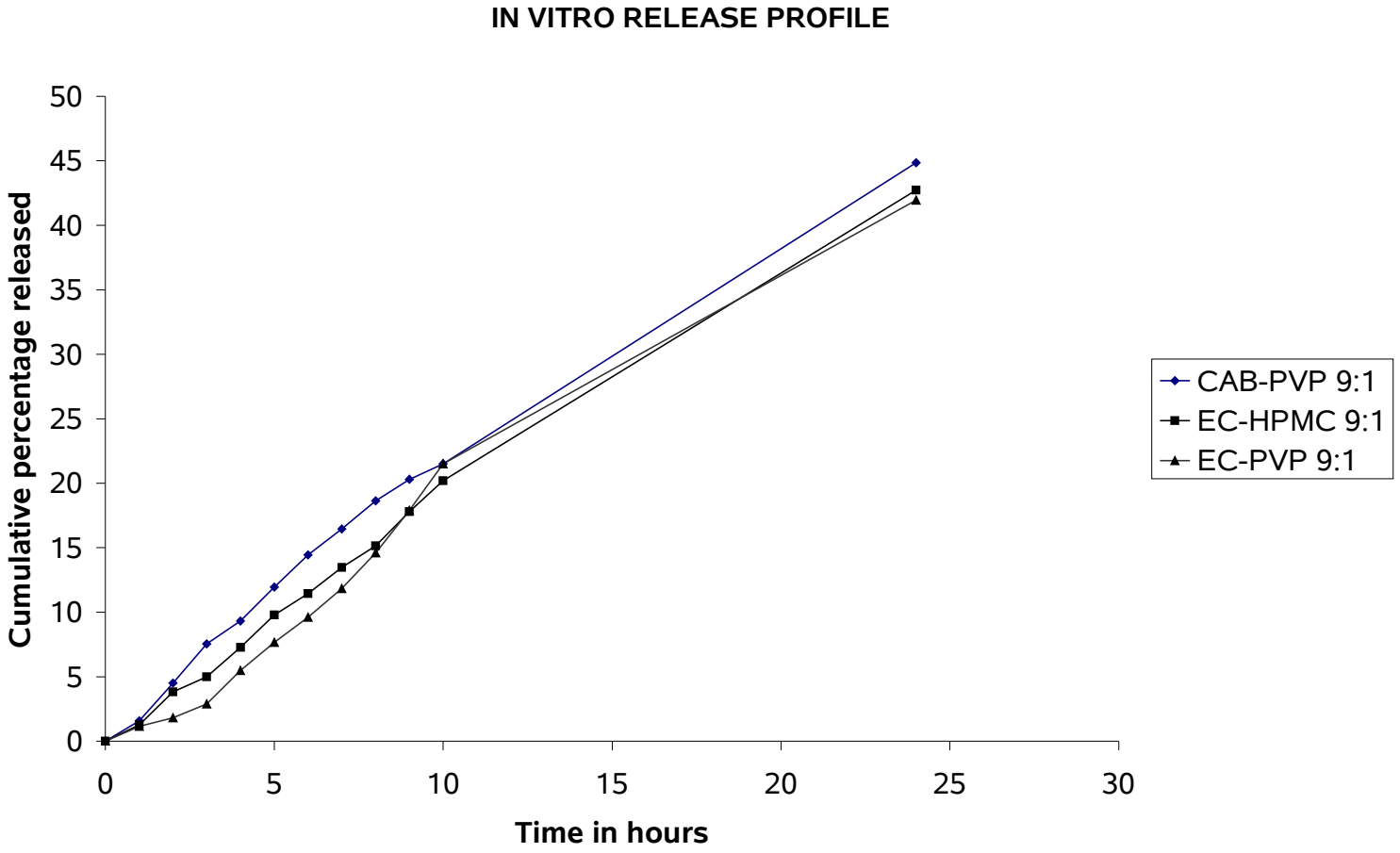

IN VITRO RELEASE PROFILE
Cumulative percentage released
Time in hours
0
5
10
15
20
25
30
35
40
45
50
CAB-PVP 9:1
EC-HPMC 9:1
EC-PVP 9:1

Table 10 Cumulative percentage released for the patches F_2, F_9 and F_{16}

Time	F_2 CAB-PVP 8:2		F_9 EC- HPMC 8:2		F_{16} EC-PVP 8:2	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	17.99±2.76	1.82	15.75±3.42	1.59	11.32±3.82	1.232
2	48.42±3.28	4.917	41.32±4.49	4.178	17.85±5.63	1.943
3	78.71±4.13	8.0	57.54±4.76	5.819	30.85±4.32	3.359
4	92.37±2.17	9.389	82.18±2.85	8.311	51.24±3.47	5.579
5	122.46±5.32	12.447	101.74±5.37	10.289	72.32±2.16	7.874
6	148.61±4.74	15.093	129.38±2.65	13.084	90.57±2.02	9.861
7	180.06±3.92	18.28	152.23±4.2	15.395	110.39±3.17	12.019
8	197.21±2.62	20.02	168.41±5.16	17.03	141.36±4.58	15.391
9	208.72±5.87	21.198	189.72±4.74	19.186	170.22±3.17	18.534
10	224.42±3.41	22.79	211.54±2.66	21.393	201.21±5.22	21.908
24	451.88±2.82	45.89	421.55±3.78	43.44	388.65±4.63	42.318

n = 3

Fig 15

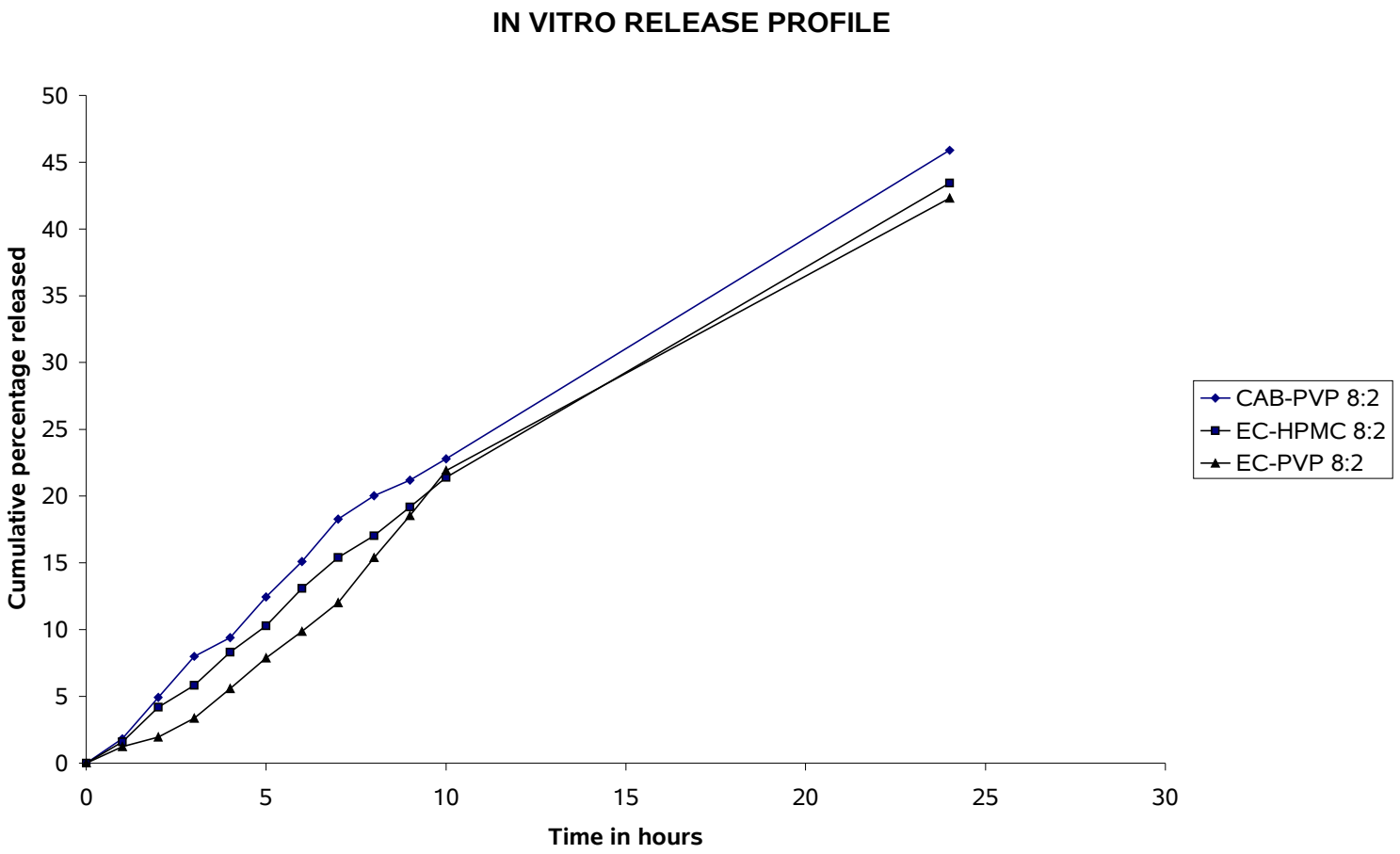

IN VITRO RELEASE PROFILE
Cumulative percentage released
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time in hours
CAB-PVP 8:2
EC-HPMC 8:2
EC-PVP 8:2

Table 11 Cumulative percentage released for the patches F_3, F_{10} and F_{17}

Time	F_3CAB-PVP 7:3		F_{10} EC- HPMC 7:3		F_{17} EC-PVP 7:3	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	20.07±5.14	2.028	18.38±3.87	1.852	11.49±2.76	1.240
2	51.24±2.75	5.177	45.75±4.66	4.610	23.37±4.42	2.523
3	81.37±4.37	8.222	61.27±3.44	6.173	31.39±2.17	3.387
4	96.27±3.92	9.728	88.45±3.67	8.912	53.27±4.35	5.752
5	129.54±5.78	13.090	105.83±2.57	10.664	78.92±2.45	8.517
6	156.32±3.46	15.79	137.94±5.43	13.899	92.45±3.28	9.983
7	183.24±4.17	18.516	166.78±3.71	16.805	113.37±3.92	12.242
8	202.57±2.55	20.46	182.42±2.48	18.381	146.57±4.74	15.828
9	214.62±3.42	21.687	198.17±3.29	19.968	173.25±3.76	19.122
10	236.47±4.68	23.89	217.45±2.76	21.911	205.61±5.42	22.204
24	463.97±2.64	46.884	432.62±5.62	43.89	392.64±4.17	42.401

n = 3

Fig 16

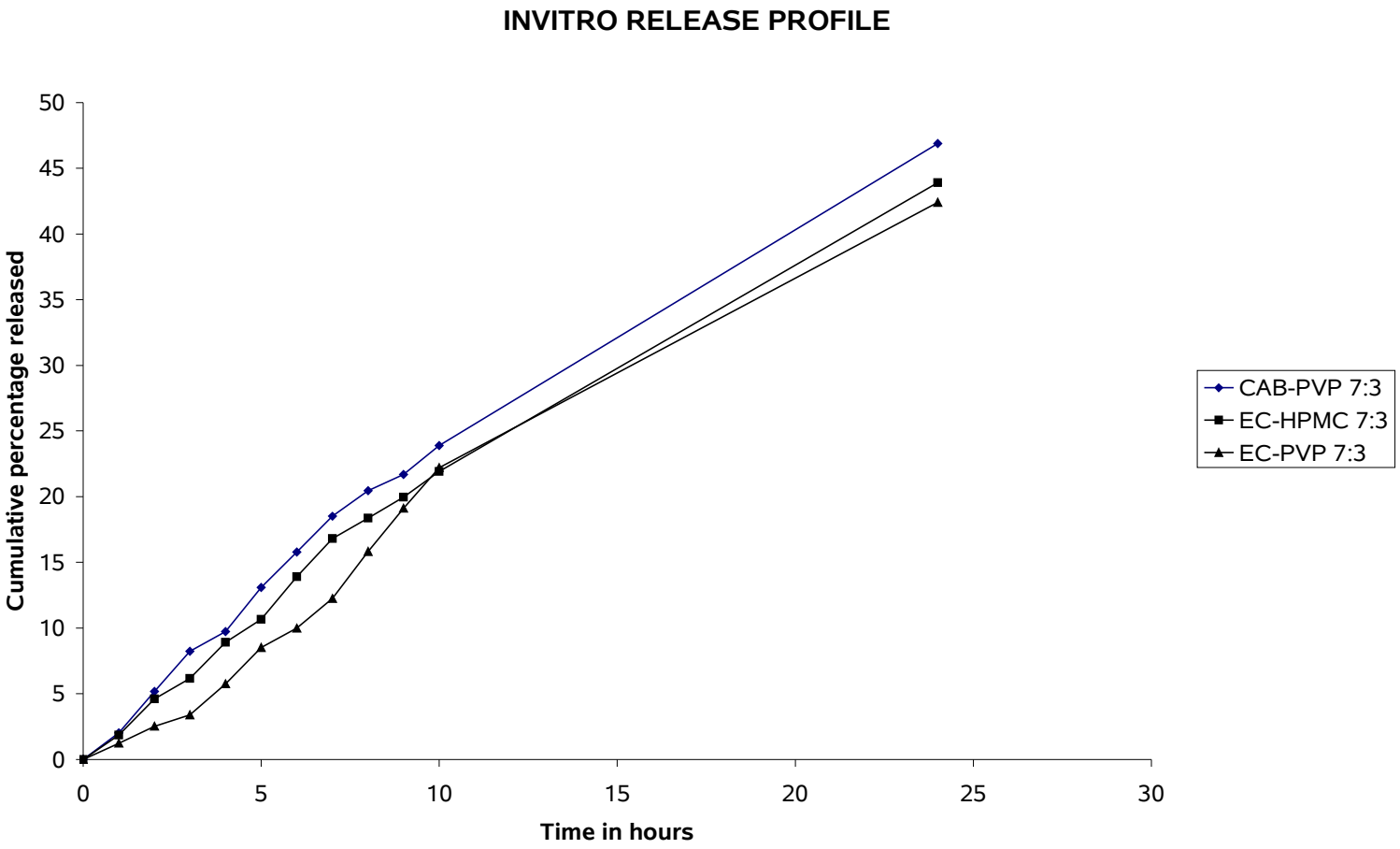

INVITRO RELEASE PROFILE
Cumulative percentage released
Time in hours
0
5
10
15
20
25
30
35
40
45
50
CAB-PVP 7:3
EC-HPMC 7:3
EC-PVP 7:3

Table 12 Cumulative percentage released for the patches F_4, F_{11} and F_{18}

Time	F_4CAB-PVP 6:4		F_{11} EC- HPMC 6:4		F_{18} EC-PVP 6:4	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	22.78±3.94	2.272	21.33±2.34	2.126	12.15±4.42	1.244
2	57.44±2.76	5.73	48.76±1.57	4.860	26.42±4.18	2.706
3	85.22±5.34	8.504	70.67±2.56	7.045	33.47±3.91	3.428
4	102.68±4.78	10.24	91.49±3.86	9.120	56.75±5.93	5.813
5	133.76±2.61	13.34	108.51±2.64	10.817	84.92±3.13	8.699
6	161.11±4.64	16.07	142.88±2.48	14.243	99.45±2.28	10.187
7	188.97±3.43	18.85	176.7±4.52	17.620	124.37±2.12	12.740
8	210.05±5.67	20.96	193.61±2.98	19.301	155.35±4.56	15.913
9	221.70±2.82	22.12	201.72±1.79	20.10	198.74±3.79	19.99
10	241.28±5.37	24.07	221.42±4.73	22.073	211.25±2.82	22.254
24	465.37±4.11	46.444	442.22±3.76	44.115	422.61±3.99	43.291

n = 3

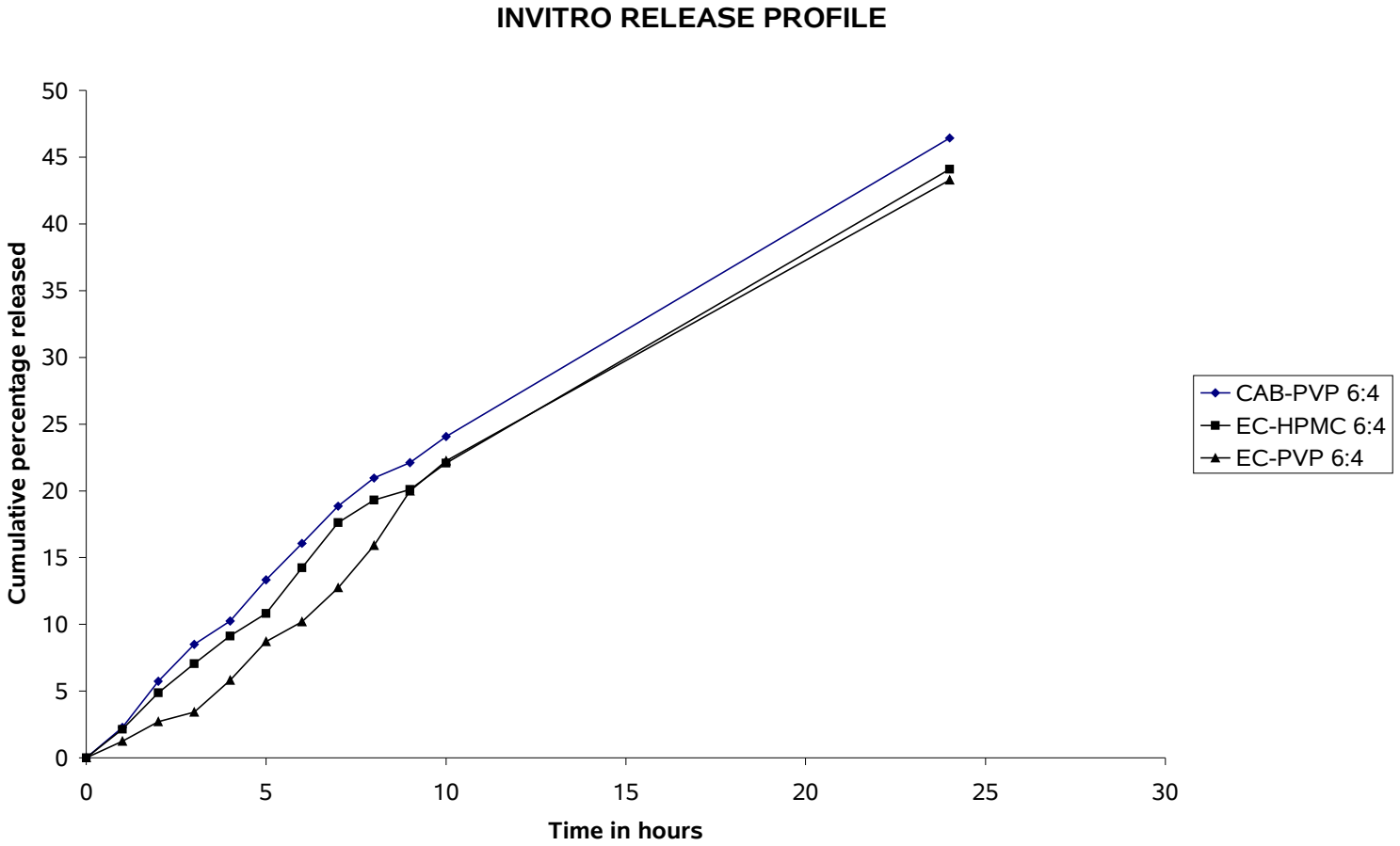

INVITRO RELEASE PROFILE
Cumulative percentage released
50
45
40
35
30
25
20
15
10
5
0
0
5
10
15
20
25
30
Time in hours
CAB-PVP 6:4
EC-HPMC 6:4
EC-PVP 6:4

Table 13 Cumulative percentage released for the patches F_5, F_{12} and F_{19}

Time	F_5CAB-PVP 5:5		F_{12} EC- HPMC 5:5		F_{19} EC-PVP 5:5	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	23.34±4.76	2.315	21.14±3.98	2.132	14.91±3.31	1.518
2	61.76±2.25	6.12	56.21±4.47	5.598	29.32±5.17	2.983
3	91.74±3.66	9.101	76.42±2.56	7.611	42.37±4.18	4.310
4	109.04±5.16	10.81	97.61±2.34	9.722	61.62±2.87	6.269
5	138.42±4.63	13.73	110.32±4.77	10.988	87.37±4.38	8.889
6	166.95±4.58	16.56	156.31±5.64	15.568	101.45±4.41	10.321
7	193.31±2.97	19.17	188.31±2.73	18.755	132.57±5.92	13.487
8	216.77±3.72	21.50	198.12±4.11	19.733	161.82±3.79	16.463
9	226.51±5.69	22.47	205.32±3.69	20.699	201.22±2.57	20.472
10	248.52±2.18	24.65	226.31±2.44	22.540	201.22±2.57	22.537
24	477.25±2.89	47.34	449.751±5.61	44.751	431.25±4.91	43.875

n = 3

Fig 18

INVITRO RELEASE PROFILE

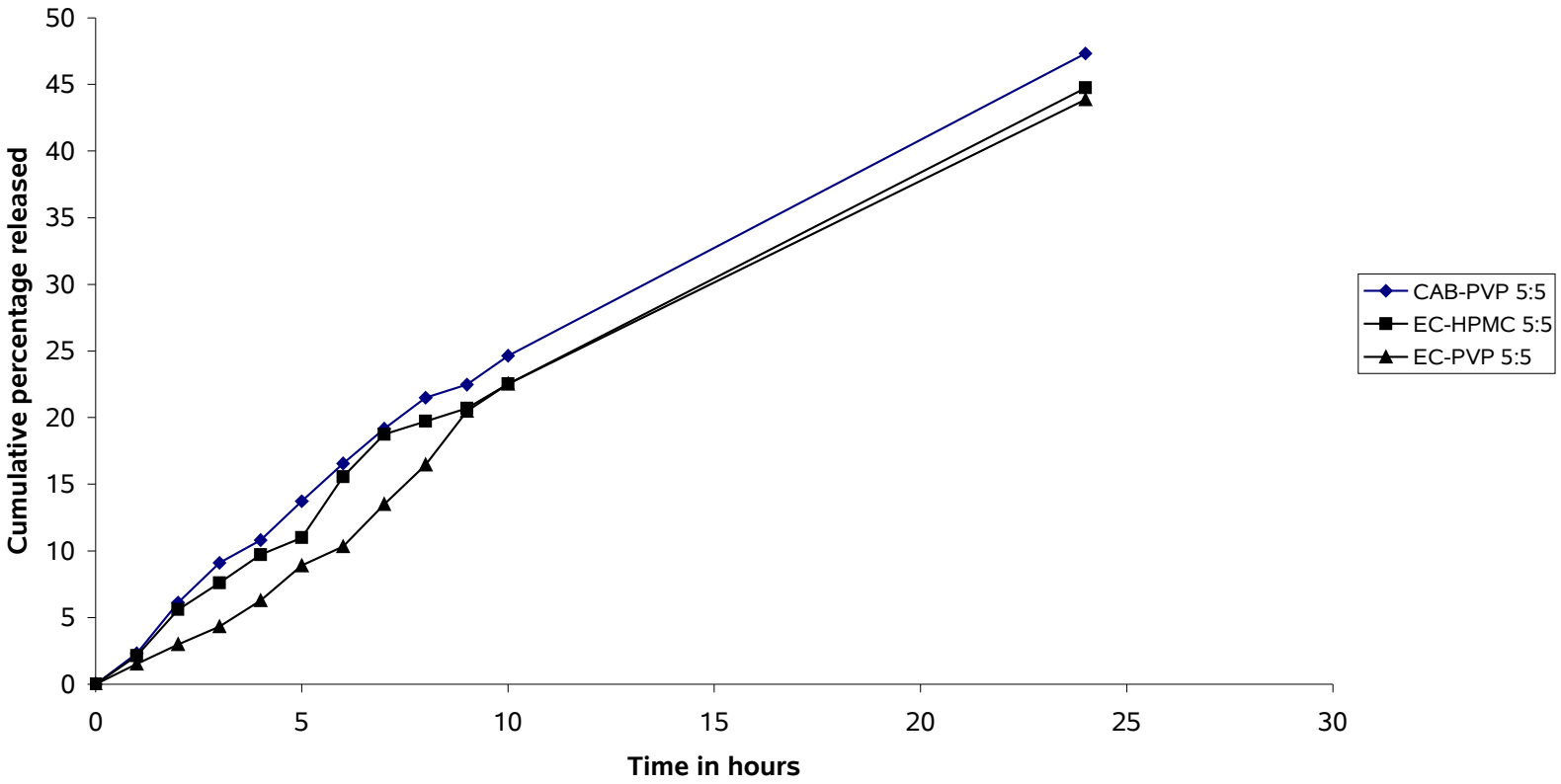


Table 14 Cumulative percentage released for the patches F_6 and F_{13}

Time	F_6CAB-PVP 4:6		F_{13} EC- HPMC 4:6	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	26.61±5.73	2.613	23.39±5.69	2.304
2	64.56±4.44	6.34	58.92±2.14	5.804
3	95.54±3.49	9.385	81.32±2.18	8.011
4	114.14±2.31	11.212	98.64±4.32	9.718
5	143.91±3.97	14.136	116.23±5.73	11.451
6	173.32±4.59	17.025	161.43±3.18	15.904
7	200.07±3.27	19.65	192.36±2.94	18.951
8	225.46±2.95	22.147	203.42±3.29	20.041
9	249.76±4.66	24.534	212.71±2.84	20.956
10	273.39±2.74	26.85	231.42±3.28	22.80
24	486.22±4.81	47.76	465.65±5.79	45.876

n=3

Fig: 19

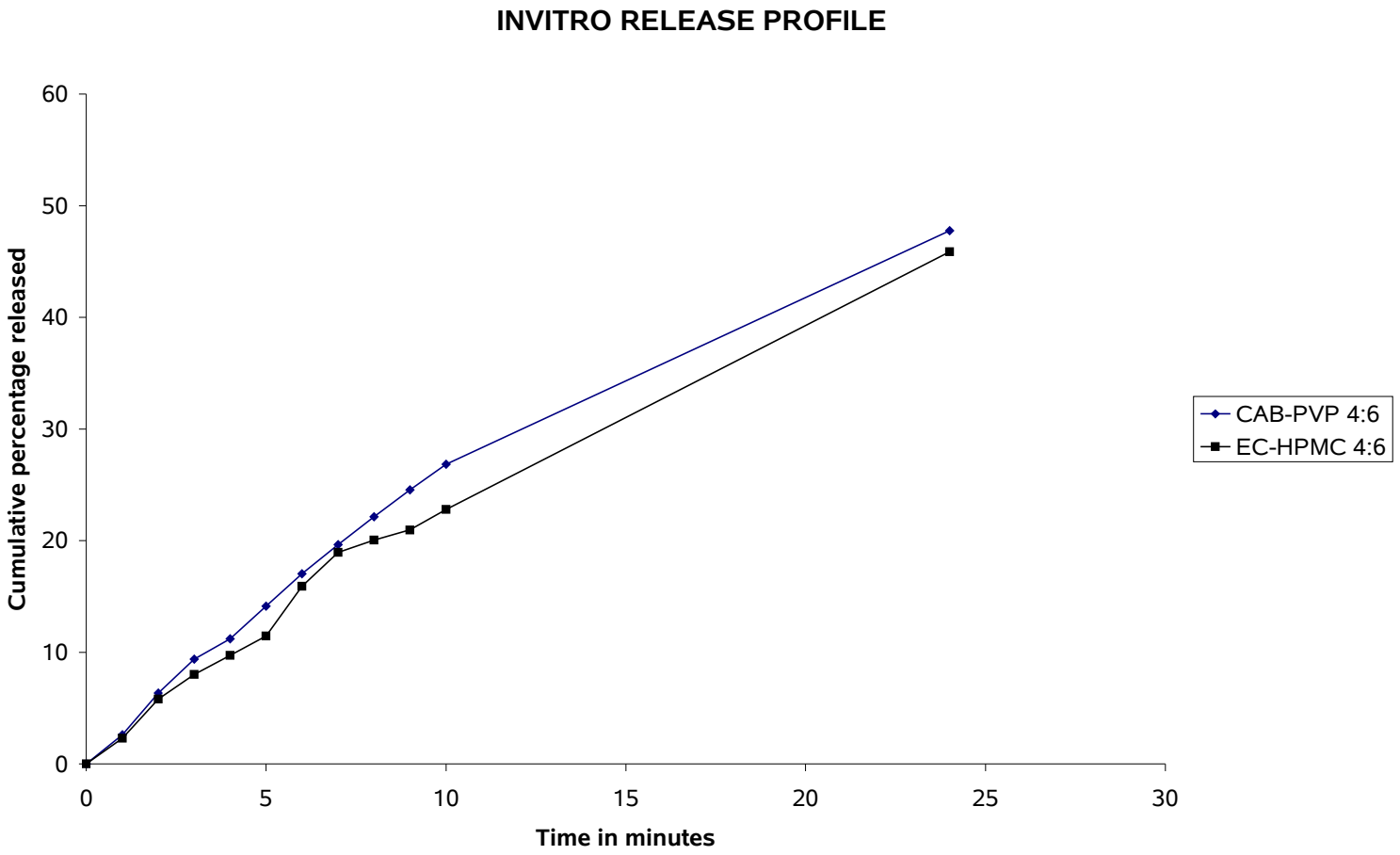
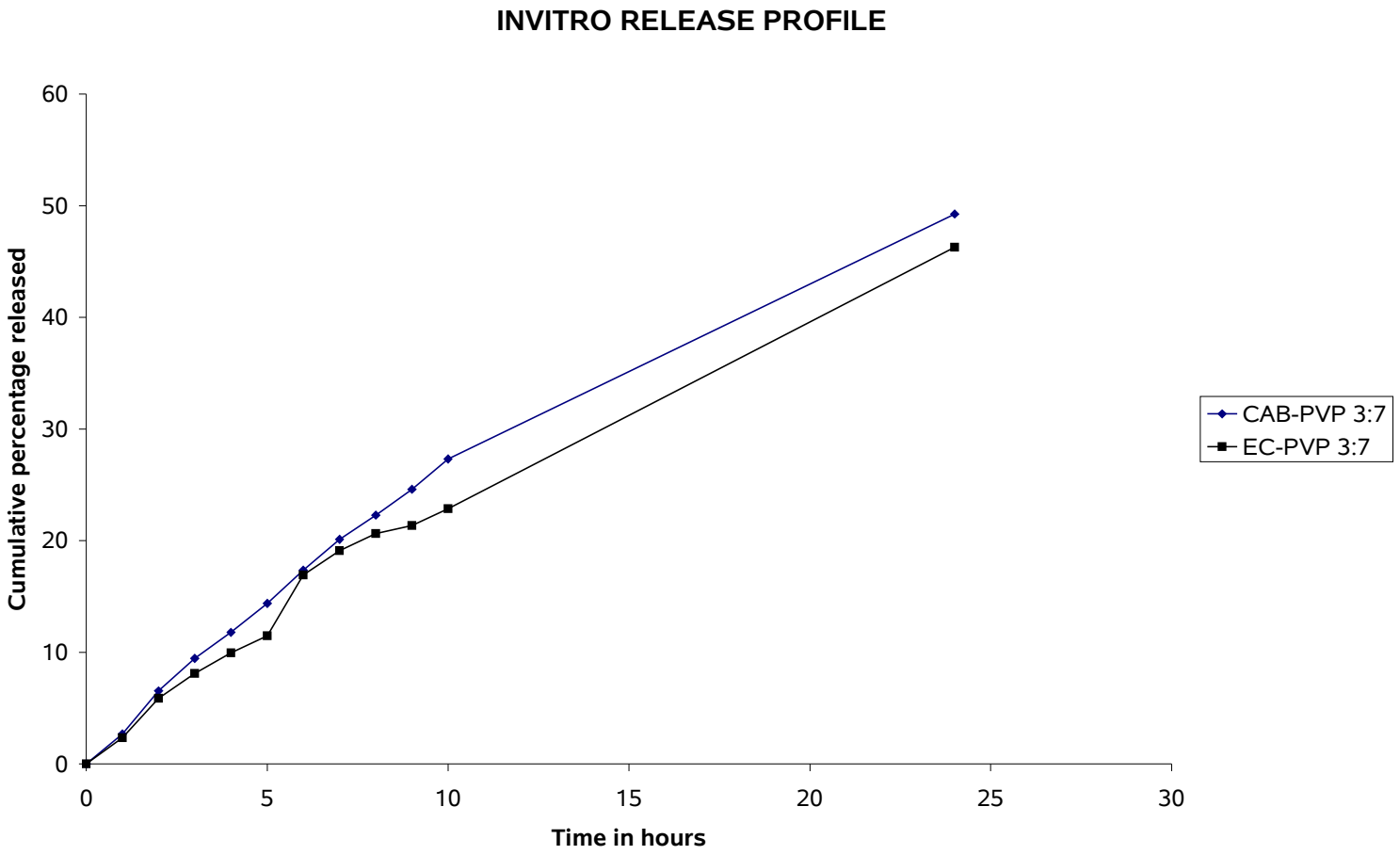

INVITRO RELEASE PROFILE
Cumulative percentage released
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time in minutes
CAB-PVP 4:6
EC-HPMC 4:6

Table 15 Cumulative percentage released for the patches F_7 and F_{14}

Time	F_7CAB-PVP 3:7		F_{14} EC- HPMC 3:7	
	Cumulative amount released µg/cm^2(±SD)	Cumulative % released	Cumulative amount released µg/cm^2(±SD)	Cumulative % released
1	27.73±2.67	2.692	24.17±5.19	2.348
2	67.37±4.94	6.540	60.31±3.32	5.861
3	97.39±2.48	9.455	83.45±4.72	8.109
4	121.42±3.26	11.788	102.37±2.91	9.948
5	147.39±4.44	14.369	118.15±4.32	11.477
6	178.61±3.53	17.340	174.27±4.38	16.935
7	201.09±3.14	20.105	196.51±2.6	19.097
8	229.59±5.61	22.290	212.76±5.68	20.619
9	253.39±3.85	24.600	219.81±3.36	21.362
10	281.42±5.39	27.322	235.24±4.37	22.861
24	507.39±4.74	49.26	476.22±3.91	46.279

n=3

Fig. 20


INVITRO RELEASE PROFILE
Cumulative percentage released
60
50
40
30
20
10
0
0
5
10
15
20
25
30
Time in hours
CAB-PVP 3:7
EC-PVP 3:7

STABILITY STUDIES

The patches F_7, F_{14} , F_{19} was taken for accelerated stability studies. By keeping it under 25^0C and 37^0C and observing the drug content and *in vitro* release for the interval of 10 days up to 30 days.

Table 16 Percentage drug content for patches F_7, F_{14} and F_{19} during accelerated stability studies.

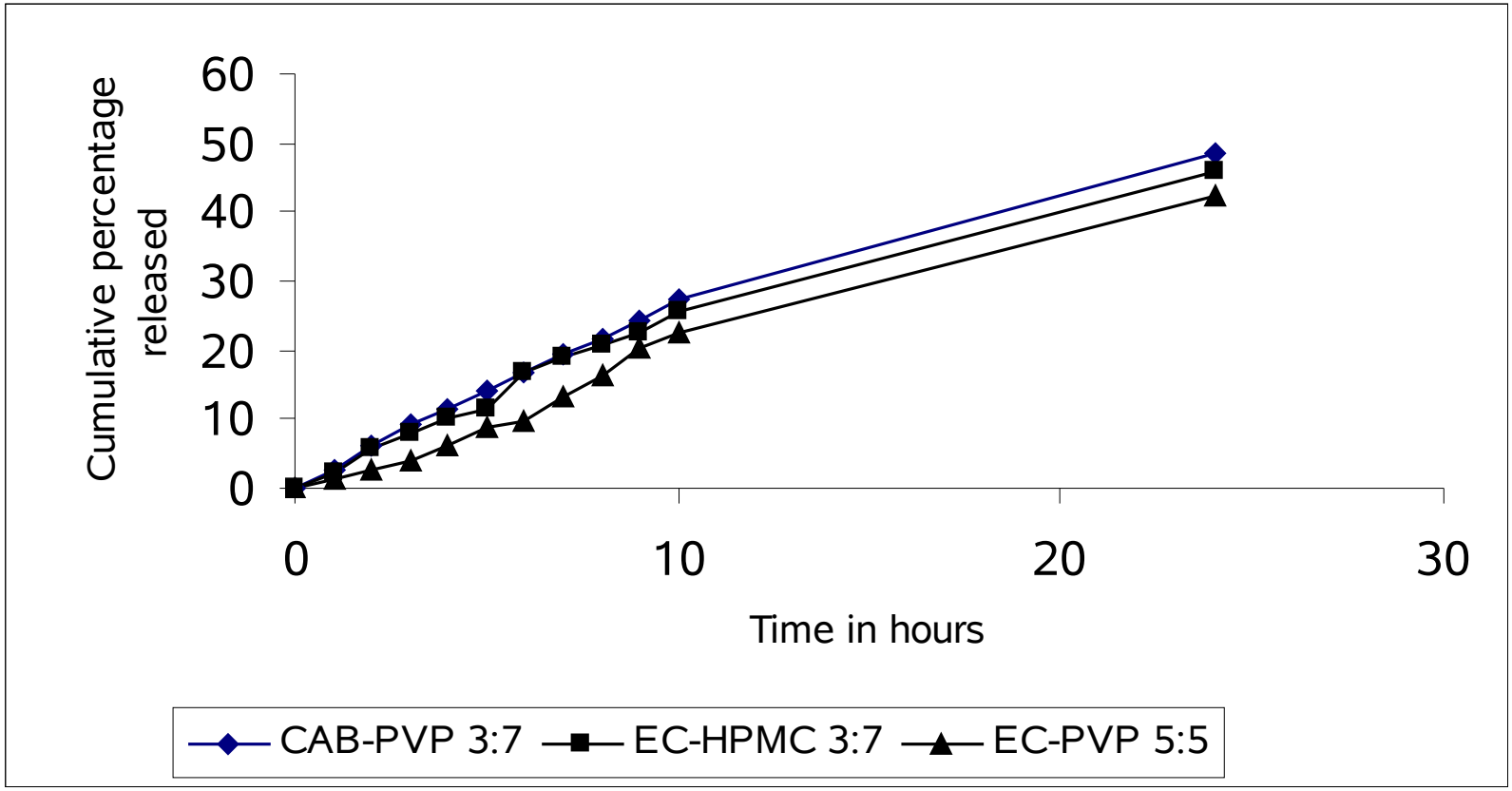
Time in days	Drug content (25^0c)			Drug content (37^0 c)		
	F_7	F_{14}	F_{19}	F_7	F_{14}	F_{19}
0	100	100	100	100	100	100
10	100	100	100	99.70	99.61	99.91
20	99.92	99.87	99.96	99.51	99.42	99.89
30	99.67	99.63	99.81	99.22	99.03	99.78

Table 17 Cumulative percentage of drug release for patches F_7, F_{14} and F_{19} during stability studies

Time	F_7 CAB-PVP 3:7		F_{14} EC-HPMC 3:7		F_{19} EC-PVP 5:5	
	Cumulative amount released in mcg/cm^2 (S.D)	Cumulative percentage released	Cumulative amount released in mcg/cm^2 (S.D)	Cumulative percentage released	Cumulative amount released in mcg/cm^2 (S.D)	Cumulative percentage released
1	26.29±1.34	2.57	23.24±3.15	2.280	12.26±	1.250±3.41
2	62.83±1.43	6.147	58.71±2.62	5.761	26.51±	2.703±2.79
3	96.54±3.21	9.446	80.42±2.47	7.892	40.76±	4.156±2.26
4	119.39±1.58	11.68	101.39±3.43	9.949	59.78±	6.095±1.72
5	142.47±2.36	13.94	116.24±1.38	11.407	86.54±	8.824±1.97
6	169.71±2.71	16.60	171.47±1.71	16.827	97.32±	9.923±2.38
7	199.76±1.19	19.545	194.51±3.54	19.088	131.68±	13.427±3.64
8	221.54±2.82	21.677	211.14±2.79	20.720	158.48±	16.159±2.89
9	247.24±3.47	24.191	230.28±2.23	22.598	197.51±	20.139±1.25
10	278.57±3.34	27.257	261.76±1.92	25.687	219.77±	23.409±2.84
24	495.39±1.64	48.47	465.34±2.19	45.663	417.68±	42.509±3.87

n = 3

Fig 21


Cumulative percentage released
60
50
40
30
20
10
0
0
10
20
30
Time in hours
CAB-PVP 3:7
EC-HPMC 3:7
EC-PVP 5:5

SUMMARY AND CONCLUSION

The purpose of the work was an attempt to develop a transdermal drug delivery system of metoprolol tartrate using three different polymer combinations i.e. CAB-PVP, EC- HPMC and EC-PVP in different ratios. Total of 19 patches were prepared out of which the CAB-PVP patches were found to have better characteristics than the other two patches.

The compatibility studies confirmed the absence of chemical interaction between the drug and other excipients employed in the formulation. They have been evaluated for physicochemical parameters like physical appearance, average weight, thickness, percent moisture content, percent moisture uptake and drug content. Release rates were found out by *in vitro* diffusion studies using Franz diffusion cell.

From the *in vitro* release results observed, it was noticed that patches prepared using CAB-PVP proved to exhibit better release characteristics. The results for the physicochemical parameters of CAB- PVP patches were also better than the other two patches containing EC- HPMC and EC- PVP.

Accelerated stability studies indicated that the formulated patches were having adequate shelf life. The primary skin irritation studies on rabbits revealed that the formulated patch is compatible with skin.

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